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JOURNAL OF THE BRITISH MEDICAL ASSOCIATION

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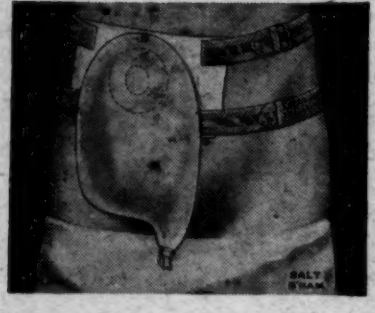

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BRITISH MEDICAL JOURNAL

LONDON SATURDAY MARCH 5 1955

TREATMENT OF ACUTE RHEUMATIC FEVER IN CHILDREN

A Co-operative Clinical Trial of A.C.T.H., Cortisone, and Aspirin

A JOINT REPORT* BY

THE RHEUMATIC FEVER WORKING PARTY OF THE MEDICAL RESEARCH COUNCIL OF GREAT BRITAIN

AND

THE SUBCOMMITTEE OF PRINCIPAL INVESTIGATORS OF THE AMERICAN COUNCIL ON RHEUMATIC FEVER AND CONGENITAL HEART DISEASE, AMERICAN HEART ASSOCIATION

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Starting in 1949, encouraging reports of A.C.T.H.† and cortisone in the treatment of acute rheumatic fever aroused hope that a more effective therapy had at last become available. Conclusions of the early and uncontrolled studies were, however, somewhat contradictory, in that some investigators reported that the hormones altered the course of acute rheumatic fever while others suggested that they merely suppressed its clinical manifestations (see bibliographies in Thorn *et al.* (1950) and Massell (1954)). At that time no data were available concerning the prevention of rheumatic heart disease by these agents, a question which could be answered only by a long follow-up study.

By early 1950 it became evident to both the Council on Rheumatic Fever and Congenital Heart Disease of the American Heart Association and the Medical Research Council of Great Britain that there was need for a controlled study of the efficacy of these hormones in comparison with the previously accepted therapy. It was also clear that no single research centre could provide, in a short period of time, enough cases to give a definitive answer. It was therefore proposed that a group of research centres should collaborate. The co-operative clinical trials of the streptomycin treatment of tuberculosis in Great Britain under the Medical Research Council and similar studies in the United States under the Veterans Administration pointed the way. Planning funds were soon made available.

There were several advantages in the establishment of a co-operative study on an international basis. It was possible that the general availability of A.C.T.H. and cortisone in the United States might seriously interfere with a strictly controlled clinical trial. Large numbers of cases would be collected rapidly. Much-needed information on the natural history of the disease in two different parts of the world would be made available.

The Committee on Criteria and Standards of the Council on Rheumatic Fever and Congenital Heart Disease, together with a group of American and Canadian rheumatic fever research workers, set up a subcommittee of principal investigators for American planning. It also established liaison with the Working Party on Rheumatic Fever of the Medical Research Council of Great Britain. Joint planning of the United Kingdom–United States Co-operative Rheumatic Fever Study was begun and the design of the study completed in a six months' period.

The trial was designed to compare the therapeutic effects of the hormones, A.C.T.H. and cortisone, with the usual treatment of rheumatic fever at the time—namely, aspirin—all patients to be treated in hospital on bed rest and protected against beta-haemolytic streptococcal

*This report is being published simultaneously in the *British Medical Journal* in the United Kingdom and in *Circulation* in the United States.

†Throughout this paper A.C.T.H. will be used to indicate corticotropin, *N.N.R.*

infection. Within the limitations imposed by the design of the study, answers were sought to two questions:

(1) What is the relative effectiveness of each of these hormones and of aspirin in altering the course of the acute disease or in suppressing its clinical manifestations?

(2) What is the relative effectiveness of these three agents in preventing rheumatic heart disease?

Information was also collected on the side-effects of the two hormones and of aspirin.

The design created and agreed upon by the principal investigators in both countries, in co-operation with the co-ordinating staff and statistical consultants, provided for diagnostic criteria, random allocation of patients to treatment groups, a uniform six-weeks therapeutic regimen, and a fixed time-pattern for observation and follow-up. It prescribed the type and frequency of clinical and laboratory observations during hospital stay and follow-up period and required reporting on specially prepared forms (see Appendix) to the co-ordinating centres in London and New York City.

This report compares the effects of the three drugs—A.C.T.H., cortisone, and aspirin—on the acute course of rheumatic fever, in children under the age of 16, through 13 weeks from the start of treatment, and on the persistence and development of rheumatic heart disease through one year.* Subsequent reports will include a similar analysis of adult patients and, after longer follow-up, of the relative effectiveness of the three drugs in the prevention of rheumatic heart disease. These extensive data should also provide much information on the natural history of the disease.

Diagnostic Criteria for Admission of a Patient to the Study

To ensure, so far as possible, that in all centres patients admitted to the trial were unquestionable cases of rheumatic fever, and of no other illness, it was necessary to specify precise diagnostic criteria. Since there are no specific diagnostic clinical symptoms or signs or laboratory tests, such criteria must be arbitrary. The criteria had to be broad enough not to exclude many genuine early cases, and yet sufficiently rigid that there should be, among competent clinicians, no reasonable doubt regarding the diagnosis.

The diagnostic criteria were based on those of T. Duckett Jones (1944), modified for the purposes of this study with his advice and assistance.† They divide the manifestations of rheumatic fever into two groups, major and minor. There were five major and five minor manifestations, defined as follows.

Major Manifestations

(1) CARDITIS, *as shown by any one of the following: (a) the development of an organic apical systolic murmur or an aortic diastolic murmur under acceptable observation‡; (b) a change of heart size of more than 15% on standard x-ray film by any standard method of measurement; (c) pericarditis revealed by a definite friction rub or by pericardial effusion; (d) congestive failure, in a patient under 25 years and in the absence of other causes, and shown by one or more of the following: (1) dyspnoea, (2) orthopnoea, (3) enlargement of the liver, (4) basal pulmonary rales, (5) increased jugular venous pressure, or (6) oedema.*

In the assessment of carditis as a criterion for entry to the trial, it was assumed in patients with no known pre-existing rheumatic heart disease or history of an attack of acute rheumatic fever, that previous to the current illness the patient's heart was of normal size and that there were no rheumatic murmurs. In other patients, observations of changes in heart size and murmurs were used in determining carditis, and recorded.

(2) POLYARTHRITIS, *as shown by pain and either limitation of active motion or tenderness, in two or more joints.*

(3) CHOREA, *with movements of at least moderate severity.*

(4) SUBCUTANEOUS NODULES.

(5) ERYTHEMA MARGINATUM (or ANNULARE).

Minor Manifestations

(1) FEVER, *defined as any temperature above 99.3° F. (37.4° C.) by mouth or 100.3° F. (38° C.) rectally, occurring at least twice in one period of 24 hours, or above 100.3° F. (38° C.) by mouth or 101.3° F. (38.5° C.) rectally, observed on any one occasion.*

(2) ELEVATED SEDIMENTATION RATE, *defined as 15 mm./hr. or above (Wintrobe (1935), corrected by the Whitby and Hines chart to a haematocrit of 45%).*

(3) EVIDENCE OF PREVIOUS STREPTOCOCCAL INFECTION, *as shown by a culture in which beta-haemolytic streptococcus predominated, or by an antistreptolysin O titre of 200 units or greater, or by a reliable history of sore throat with fever preceding the onset of illness by an interval of one week to one month.*

(4) AN INCREASED P–R INTERVAL, *defined as a value at least 0.04 sec. beyond those given in the Ashman and Hull (1947) tables for ages under 16.*

(5) A RELIABLE HISTORY OF RHEUMATIC FEVER, *as defined in these criteria or* EVIDENCE OF PRE-EXISTING RHEUMATIC HEART DISEASE—*namely, an apical organic systolic murmur, an apical diastolic or a basal diastolic murmur.*

These criteria having been specified, it was ruled that to be admitted to the study the patient must (*a*) at some time during the illness which brought him to the centre have exhibited at least two major manifestations *or* one major and two minor manifestations, and (*b*) on the first day of the allotted therapy show evidence of any one major manifestation *or* of any two of the three following minor manifestations—fever, elevated sedimentation rate, increased P–R interval.

It was arbitrarily decided that an interval of at least three months with no rheumatic activity must have preceded the present illness to justify its being called a new attack. With any shorter interval of time between the present and a previous illness, the present illness was held to be an exacerbation of symptoms of the previous attack and not a new attack. In such instances, the date of onset was referred back to the beginning of the illness.§

Patients who had had previous hormone therapy were excluded from the trial (a single test dose previously administered was not regarded as therapy). If a patient was receiving salicylate therapy, that treatment was discontinued upon admission to the hospital, before the patient was considered for inclusion. If such a patient subsequently satisfied the criteria he was eligible and admitted in the ordinary way.

*The one year follow-up data represent observations made at a calendar year from the end of the nine-weeks period of treatment and observation (61 weeks from the start of therapy).

†These modified criteria are not necessarily applicable for general use by the practising physician, particularly in questionable cases where continued observation of patients may be necessary for definitive diagnosis.

‡The development of an apical mid-diastolic murmur was also used for the diagnosis of carditis in U.K. centres, but there was only one case in which the diagnosis of carditis rested solely on this murmur, and this case was eligible under other criteria.

§"Onset" was defined as the date of the first observation of any major manifestation or any minor manifestation that appeared to be related in a continuous time sequence to the development of any major manifestation.

Treatment Plan

Dosage Schedules

The dosage schedules of A.C.T.H., cortisone, and aspirin were based (in 1950) on published studies, modified by reports from investigators to Armour Laboratories and Merck and Company. From such information, a dosage was selected to be effective for a period of administration short enough to indicate whether the acute attack had been differentially shortened by any one of the three drugs. Provision was made for decreasing the dosage if toxic manifestations appeared and for "tapering off" so that cessation of therapy would not be abrupt.

While the same hormone dosage was used for all patients, the dosage schedule of aspirin was calculated on the basis of body weight. Cortisone and A.C.T.H. were administered intramuscularly, while aspirin was given by mouth.

The dosage schedules were:

*A.C.T.H.**—All cases U.K. and eight cases U.S.†: a total daily dosage of 80 U.S.P. units for the first four days, 60 units for the next three days, 40 units for the second and third weeks, 30 units for the fourth and fifth weeks, and 20 units for the sixth week, administered every six hours.

All but eight cases U.S.: a total daily dosage of 120 U.S.P. units for the first four days, 100 units for the next three days, 80 units for the second week, 60 units for the third week, 40 units for the fourth and fifth weeks, 20 units for the sixth week, administered every six hours.

The A.C.T.H. dosage in the U.S. was increased early in the study, because with the relatively poor methods available for lot standardization and the lack of dramatic response in the first few cases treated, it was held possible that optimum dosage was not being administered. In regard to the question of "adequacy" of hormone dosage, it is of interest that practically all cases receiving A.C.T.H. or cortisone had side-effects, the details of which are presented later.

Cortisone.‡—A total daily dosage of 300 mg. for the first day, 200 mg. for the next four days, 100 mg. for the remainder of the first three weeks, 75 mg. for the fourth and fifth weeks, 50 mg. for the sixth week.

In the few cases where the hormone dosage was reduced because of undesirable side-effects, the percentage stepwise reduction in dosage thereafter remained unchanged.

Aspirin (acetylsalicylic acid, U.S.P. or B.P., 0.3 g. (5 gr.) tablets).—A total daily dosage of 60 mg. (1 gr.) per lb. of body weight (140 mg. per kg.) or 10 g. (150 gr.) total dosage, whichever was less, for the first two days; 40 mg. (⅔ gr.) per lb. (100 mg. per kg.), or 10 g. (150 gr.), whichever was less, for the next five days; 30 mg. (½ gr.) per lb. (70 mg. per kg.) for the remainder of the six weeks. Administered every four hours for 48 hours, every six hours thereafter. Aspirin was administered without bicarbonate of soda.

Patients unable to tolerate aspirin in the scheduled dosage received the largest amounts that they could tolerate as determined by the investigator. This occurred mainly in the older patients where the body-weight dosage produced side-effects. Conversely, because of the weight-dosage formula, small children did not receive aspirin up to the limit of tolerance.§

During the three-weeks observation period following the six-weeks course of therapy, none of these drugs was administered unless the investigator believed that the patient's condition was so poor as to endanger life or the polyarthritis so painful that it could not otherwise be controlled. In such cases, re-treatment was given for a period of four weeks, using the same drug and dosage as in the first four weeks of initial therapy; it was followed by a three-weeks observation period as before.

If re-treatment was necessary at any time during the three months following the original course of therapy, then the above four-weeks re-treatment scheme was followed. No patient was re-treated unless he demonstrated rheumatic activity sufficient to have brought him into the study initially.

If after three months without activity the patient developed a new attack of rheumatic fever, he was treated as in the original course—that is, for six weeks on the same drug and dosage, followed by a three-weeks period of observation.

Auxiliary Therapy

Sodium and Potassium Intake.—To minimize salt retention in hormone-treated patients, and to maintain comparability among the three treatment groups, the dietary intake of sodium was restricted to less than 2 g. per day for all patients for at least four weeks. All patients received added potassium chloride by mouth daily, 2 g. for those weighing less than 60 lb. (27.2 kg.) and 3 g. for those 60 lb. (27.2 kg.) or more, except that those few who developed oliguria due to congestive failure received no added potassium. Serum potassium levels were estimated weekly.

Streptococcal Prophylaxis.—Every effort was made through streptococcal prophylaxis to prevent recurrent attacks of rheumatic fever which would introduce an additional variable in the study. All patients, upon admission to the study and on the fourth, seventh, and tenth days of treatment, received procaine penicillin G in aluminium monostearate intramuscularly, 300,000 units for those weighing less than 60 lb. (27.2 kg.), 600,000 units for those 60 lb. (27.2 kg.) or more.‖ On the 14th day after admission to the study, and continuously thereafter, sulphadiazine was administered in a dose of ½ g. per day to those weighing less than 60 lb. (27.2 kg.) and 1 g. per day to those weighing 60 lb. (27.2 kg.) or more. (In a few patients, oral penicillin in a dose of 100,000 units twice a day was substituted when sensitivity to sulphadiazine developed.) Sera were drawn for determination of antistreptolysin-O titres (Massell and Miller's unpublished technique modified from Hodge and Swift, 1933) at weeks 0, 5, 9, and 13, and at each follow-up examination, to detect intercurrent streptococcal infection.

In addition to this routine, throat cultures were made on all patients on admission to hospital, and thereafter whenever there was indication of a throat infection. Those with positive cultures received penicillin therapy, as prescribed by the investigator.

Other Therapy.—All but a few patients were kept at bed rest for the nine weeks of therapy and observation. In a few cases of chorea, sedatives were necessary. No antirheumatic drugs other than those allocated for the study were given. Therapy necessary for any complicating illness was recorded.

Allocation of Patients to Treatment

Patients on admission to the study were divided into two age groups, 0 to 15 years and 16 and over, and into three groups according to the length of time in each case between the date of onset of the attack and the date at which therapy began. The three duration-from-onset groups were (1) 14 days or less; (2) 15 to 42 days; (3) 43 days and over.

For each of these three duration groups, within each age group, and separately for each treatment centre, the three treatments, A.C.T.H., cortisone, and aspirin, were listed in

*A.C.T.H., donated by Armour Laboratories, was in three lots of water-soluble material standardized on both animals and human beings. All the U.K. cases were treated with one lot (K-50601R), while most of the U.S. cases received a second lot (J-24109R), although a few were treated with a third lot (L-56702). The U.S.P. unit is expressed as a milligram equivalent of A.C.T.H. lot number LA-IA.

†One Canadian centre took part in the trial, but for easy reference the term "U.S." is used to include all North American centres.

‡Cortisone, donated by Merck and Company, was the regular commercial preparation for intramuscular use—namely, the acetate of 17-hydroxy-11-dehydrocorticosterone, suspended in a vehicle consisting of sodium carboxymethyl cellulose, Tween 80, and 1.5% benzyl alcohol in isotonic saline.

§Salicylate blood levels determined in two U.S. centres showed a positive correlation with body weight; lower blood levels found in one U.K. centre revealed no such relationship.

‖At the House of the Good Samaritan (Boston) a variable dosage schedule was used.

TABLE 1.—*Details of 15 Cases Admitted to the Study in Which the Treatment and Observation Schedule was not Followed, with Reference to Their Inclusion or Exclusion From the Analysis.*

Treatment Group	Treatment Stopped (5 Cases)	Treatment Changed (5 Cases)	Re-treatment (4 Cases)	Treatment Incomplete (1 Case)
A.C.T.H. (4 cases) ..	(1) U.S. gastric haemorrhage 6th day. Excluded (2) U.S. renal haemorrhage 21st day. Included (3) U.S. toxicity[1] 27th day. Included (4) U.K. toxicity[2] 32nd day. Included			
Cortisone (3 cases) ..			(11) U.S. re-treated 48th day. Included (12) U.S. re-treated 50th day. Included	(15) U.S. patient left hospital 12th day.[3] Excluded
Aspirin (8 cases) ..	(5) U.S. discharged from hospital 41st day.[4] Included	(6) U.S. in failure. Changed to A.C.T.H. 8th day. Excluded (7) U.S. carditis and failure. Changed to A.C.T.H. 28th day. Included under aspirin (8) U.S. carditis. Changed to A.C.T.H. 28th day. Included under aspirin (9) U.S. carditis. Changed to cortisone 50th day. Included under aspirin (10) U.K. pericarditis and failure. Changed to cortisone 51st day. Included under aspirin	(13) U.S. re-treated 45th day. Included (14) U.S. re-treated 58th day. Included	

[1] Unusually rapid weight gain and enlargement of liver not responding to mercurial diuretics. [2] Too rapid development of moonface. [3] Family moved to another city. [4] Child was an unmanageable behaviour problem.

random order for as many patients as were likely to be admitted, using random sampling numbers and keeping the numbers of patients on the three treatments approximately equal in each centre. The co-ordinating centre in each country issued serially numbered and sealed envelopes to the treatment centres. Thus, on admission of a patient of given age and specified duration-from-onset group, the investigator at the treatment centre had merely to open the next available envelope for that particular group to find a statement of the treatment to be applied. He was therefore unable to predict the treatment for his next case. The allocation was both "blind" and random.*

The admission report on the patient, and the assignment envelope, were then sent to the co-ordinating centre. If for any special reason the investigator decided in advance that a patient fulfilling the criteria should not be admitted to the study, no envelope was opened. In every such case, however, an admission report was required, together with an explanation as to why the patient had not been admitted. Six such cases were reported in the U.S.; none in the U.K.†

The Study Sample

In all, 505 children under 16 years of age were admitted to the study—242 in the U.K. between March 2, 1951, and October 6, 1952, and 263 in the U.S. between January 15, 1951, and June 15, 1952. Four of these cases were subsequently excluded when their illness proved to be a disease other than rheumatic fever. These were a case on cortisone (U.K.) of Henoch–Schönlein purpura, a case on aspirin (U.K.) of tuberculous meningitis, a case on A.C.T.H. (U.S.) of lupus erythematosus disseminatus, and a case on A.C.T.H. (U.S.) of salmonella infection. In another case on A.C.T.H. (U.S.) there was *x*-ray evidence of tuberculous infection superimposed upon the rheumatic fever, and hormone treatment was therefore withheld. These five exclusions present no problem.

In the remaining 500 patients (240 U.K., 260 U.S.) there was only the small number of 15, or 3%, in whom the prescribed treatment and observation schedule was not fully carried out (2 U.K., 13 U.S.). Table 1 shows their nature and the action taken with regard to them. Only three (Cases 1, 6, and 15) have been wholly excluded from the statistical analysis of the trial, since their treatment with the allotted drug was very brief (6, 8, and 12 days). All other cases had been treated for three weeks or longer. Three of them (Cases 2, 3, and 4) fall within the original provision for a reduction of dosage when essential, and four (Cases 11, 12, 13, and 14) within the provisions for re-treatment in active cases. Such patients, together with one (Case 5) that left the hospital after the six weeks of therapy, can be included under the allotted therapy without any difficulty.

There remain four aspirin cases in which, on account of the severity of the illness, the investigator administered hormone treatment. In two (Cases 7 and 8) a change to A.C.T.H. was made during the treatment period (on the 28th day); in two, treatment with cortisone was instituted during the observation period (on the 50th and 51st days), after completion of the aspirin treatment. It was thought better to continue these cases in the aspirin group in spite of the change of treatment, since the exclusion of these four cases from the analysis at these points of time would make the picture of the aspirin group somewhat too favourable, since severely ill cases were being artificially removed from it.

Altogether, it is clear that these three exclusions, four changes of the allotted treatment, and eight variations of the treatment schedule can have had no appreciable effect upon the results of the trial.

Two U.S. and four U.K. patients died during the first year and are included in the analysis.

Taken as a whole, the 497 cases under age 16 show the following features. There were, altogether, 14 cases (3%) aged 3 or 4 years, 200 (40%) aged 5 to 9 years, and 283 (57%) aged 10 to 15 years. In just over one-half (255) the allotted therapy was begun within 14 days of the onset of the attack, and a more detailed analysis shows that 149, or 60%, of these "early" cases were treated within one week of onset. In nearly two-thirds (327 cases) there was neither history of a previous attack of rheumatic fever nor evidence of pre-existing rheumatic heart disease. Only 128

*In a few centres, for varying durations of time, the investigators wished to withhold some patients for other studies. In these instances a predetermined proportion of the envelopes contained, as an instruction, "free case." Such exclusions, therefore, were also "blind" and randomly determined, and could not bias the group brought into the study.

†These six cases were: one, with schizoid personality, considered unsuitable for the trial; one, excluded because his private physician insisted upon cortisone therapy; and four severe cases excluded in one centre under provision of the protocol—namely, "If in the opinion of the principal investigator, the patient is severely ill to the point where his life is in danger, that patient may be removed from any group and given therapy at the discretion of the investigator." These four cases were treated with A.C.T.H. as follows: (1) a 12-year-old boy in a sixth attack with acute carditis, mitral insufficiency, and congestive failure made a smooth recovery without residual heart disease; (2) a 9-year-old girl in a second attack with residual heart disease, mitral insufficiency, and congestive failure made a gradual but unremarkable recovery; (3) a 12-year-old girl in a second attack, with residual heart disease, acute carditis, mitral insufficiency, and congestive failure, made, after a stormy course, a slow recovery with persistence of chronic heart disease with increasing cardiac enlargement; and (4) a 9-year-old boy in a first attack with mitral insufficiency, pericarditis, and congestive failure died after seven days of treatment.

or approximately one-quarter, of the 497 cases were in fact definitely diagnosed as having pre-existing rheumatic heart disease at the start of therapy. Mitral stenosis as shown by an apical pre-systolic murmur was reported in only 16 cases. In general, therefore, the group contained a large proportion of cases still in the early stages of the disease.

Comparability of Treatment Groups at Start of Therapy

The method of allocation ensured that in each treatment group there was approximately the same number of cases with regard to the duration from onset of attack to start of therapy. Thus, there were on A.C.T.H., cortisone, and aspirin, respectively, 86, 85, and 84 "early" cases (0 to 14 days); 47, 45, and 46 "medium" cases (15 to 42 days); and 29, 37, and 38 "late" cases (43 days or more) (Table 2).

TABLE 2.—*Comparison of Treatment Groups at Start of Therapy: Duration of Illness from Onset, Sex, Mean Age, and Mean Weight*

Treatment Group	Total Cases	Duration from Onset			Sex		Mean Age (Years)	Mean Weight (lb.)
		0–14 Days	15–42 Days	43+ Days	M	F		
U.K.:								
A.C.T.H.	80	39	27	14	40	40	10·0	66·0
Cortisone	80	38	25	17	34	46	9·9	63·6
Aspirin ..	80	32	27	21	40	40	9·6	64·4
Total ..	240	109	79	52	114	126	9·8	64·7
U.S.:								
A.C.T.H.	82	47	20	15	51	31	9·9	71·4
Cortisone	87	47	20	20	45	42	10·1	71·7
Aspirin ..	88	52	19	17	49	39	10·2	73·6
Total ..	257	146	59	52	145	112	10·1	72·2
U.K. and U.S.:								
A.C.T.H.	**162**	**86**	**47**	**29**	**91**	**71**	**10·0**	**68·8**
Cortisone	**167**	**85**	**45**	**37**	**79**	**88**	**10·0**	**67·9**
Aspirin ..	**168**	**84**	**46**	**38**	**89**	**79**	**9·9**	**69·2**
Total ..	**497**	**255**	**138**	**104**	**259**	**238**	**10·0**	**68·6**

The average age and mean body weight in the three treatment groups were almost identical, and the sex distribution was reasonably alike. In general, it is clear that the balance produced by the design of the study permits amalgamation of the duration-from-onset groups and of the data for the two countries.

Clinical features of the three treatment groups at the start of therapy are compared in Table 3. With regard to the first item, temperature, it should be noted that oral temperatures were taken in the U.K. (except at one centre) and rectal temperatures in the U.S. (except at one centre). An arbitrary correction of each oral reading was made by the addition of 1° F., and the tabulations are of the maximum "rectal temperature" recorded on each day. As the distribution of patients in each centre was evenly divided among the three treatment groups, the comparison between treatments should not be biased, even though the arbitrary temperature correction may be imperfect. It will be seen that at the start of therapy there was a larger proportion of U.S. cases (57.6%) with a rectal temperature of 100.4° F. (38° C.) or above than of U.K. cases (45.4%). This difference may be real, but it is possible that the addition of 1° F. to the oral temperature may not make the latter entirely equivalent to the rectal temperatures taken in the U.S.

The proportion of cases initially febrile (those with a temperature of 100.4° F. or greater) among the three treatment groups is dependent upon whether comparison is made on the first day of treatment or on the day before treatment was begun. On the first day of treatment there was a smaller proportion of cases febrile in the aspirin group (40.5%) than in the cortisone (61.1%) or the A.C.T.H. (53.7%) group. These differences were in part due to the more immediate antipyretic effect of aspirin in comparison with A.C.T.H. and the slowly absorbed intramuscular cortisone. This is borne out by the proportions of cases febrile on the day before therapy was started in the A.C.T.H. (61.7%), cortisone (58.1%), and aspirin (53.0%) groups.

The pulse during sleep and the erythrocyte sedimentation rates reveal no material difference (Table 3). Their mean values also showed no real differences, the average pulse during sleep being 93, 93, and 90, and the average E.S.R. 46.7, 46.2, and 45.1, for the A.C.T.H., cortisone, and aspirin groups respectively.

Within each country, the treatment groups do not differ appreciably in their incidence of joint involvement, subcutaneous nodules, and erythema marginatum, but there appears to be some difference in these respects between the two countries. The proportion of cases showing these signs (Table 3) were: joint involvement U.K. 36.7%, U.S. 49.4%; subcutaneous nodules U.K. 21.7%, U.S. 7.4%; erythema marginatum U.K. 7.9%, U.S. 3.9%. The last difference might well be due to chance, but the first two (joint involvement and subcutaneous nodules) are statistically significant ($P<0.05$). On the other hand, subdivision of these cases into early, medium, or late (Tables 10 and 15) suggests that there is no real difference between the two countries in the incidence of joint involvement. Nodules were observed more frequently in the U.K. at each stage, and particularly in the late cases.

TABLE 3.—*Comparison of Treatment Groups at Start of Therapy: Percentage with Specified Symptoms*

		Treatment Group			Total
		A.C.T.H.	Cortisone	Aspirin	
Number of cases	U.K.	80	80	80	240
	U.S.	82	87	88	257
	U.K. and U.S.	**162**	**167**	**168**	**497**
Temperature 100·4° F. (38° C.) or more (rectal)	U.K.	47·5	51·2	37·5	45·4
	U.S.	59·8	70·1	43·2	57·6
	U.K. and U.S.	**53·7**	**61·1**	**40·5**	**51·7**
Pulse during sleep 100 or more per minute	U.K.	41·8	33·3	34·6	36·6
	U.S.	29·2	36·0	26·1	30·6
	U.K. and U.S.	**35·8**	**34·6**	**30·6**	**33·7**
E.S.R. 20 mm./hr. or more	U.K.	87·5	86·2	88·8	87·5
	U.S.	96·3	93·8	94·1	94·7
	U.K. and U.S.	**91·9**	**90·0**	**91·5**	**91·2**
Joint involvement	U.K.	33·8	36·2	40·0	36·7
	U.S.	43·9	56·3	47·7	49·4
	U.K. and U.S.	**38·9**	**46·7**	**44·0**	**43·3**
Subcutaneous nodules	U.K.	22·5	23·8	18·8	21·7
	U.S.	9·8	6·9	5·7	7·4
	U.K. and U.S.	**16·0**	**15·0**	**11·9**	**14·3**
Chorea	U.K.	8·8	13·8	22·5	15·0
	U.S.	2·4	9·2	9·1	7·0
	U.K. and U.S.	**5·6**	**11·4**	**15·5**	**10·9**
Erythema marginatum	U.K.	10·0	8·8	5·0	7·9
	U.S.	4·9	4·6	2·3	3·9
	U.K. and U.S.	**7·4**	**6·6**	**3·6**	**5·8**
Pre-existing rheumatic heart disease	U.K.	31·2	32·5	31·2	31·7
	U.S.	28·0	14·9	18·2	20·2
	U.K. and U.S.	**29·6**	**23·4**	**24·4**	**25·8**
Pericarditis	U.K.	10·0	16·2	5·0	10·4
	U.S.	6·1	3·4	5·7	5·1
	U.K. and U.S.	**8·0**	**9·6**	**5·4**	**7·6**
Congestive failure	U.K.	12·5	10·0	3·8	8·8
	U.S.	15·9	8·0	8·0	10·5
	U.K. and U.S.	**14·2**	**9·0**	**6·0**	**9·7**
Cardiothoracic ratio of 0·55 or more	U.K.	21·5	26·0	13·3	20·3
	U.S.	22·5	11·8	10·5	14·7
	U.K. and U.S.	**22·0**	**18·5**	**11·8**	**17·4**
Atrioventricular conduction time of 0·18 sec. or more	U.K.	32·5	30·1	24·4	28·9
	U.S.	34·2	38·3	32·1	34·9
	U.K. and U.S.	**33·3**	**34·4**	**28·3**	**32·0**
No organic murmur	U.K.	20·0	13·8	17·5	17·1
	U.S.	26·8	33·3	36·4	32·3
	U.K. and U.S.	**23·5**	**24·0**	**27·4**	**24·9**
Apical systolic murmur	U.K.	75·0	77·5	73·8	75·4
	U.S.	69·5	64·4	59·1	64·2
	U.K. and U.S.	**72·2**	**70·7**	**66·1**	**69·6**
Apical mid-diastolic murmur	U.K.	48·8	46·2	45·0	46·7
	U.S.	34·1	23·0	25·0	27·2
	U.K. and U.S.	**41·4**	**34·1**	**34·5**	**36·6**
Basal diastolic murmur	U.K.	38·8	35·0	33·8	35·8
	U.S.	12·2	12·6	11·4	12·1
	U.K. and U.S.	**25·3**	**23·4**	**22·0**	**23·5**
Apical presystolic murmur	U.K.	5·0	2·5	1·3	2·9
	U.S.	4·9	3·4	2·3	3·5
	U.K. and U.S.	**4·9**	**3·0**	**1·8**	**3·2**

Returning to Table 3, chorea was recorded more frequently in the U.K.; in both countries chance factors brought fewer cases into the A.C.T.H. group and more into the aspirin. Thus in the total group of 162 on A.C.T.H., 167 on cortisone, and 168 on aspirin there were 9, 19, and 26 cases with chorea as a presenting symptom. Severe cases, however, numbered only four, two, and five.

For a general picture of the status of the heart at start of therapy, the 497 cases have been divided (Table 4) into groups depending on the presence or absence of pre-existing rheumatic heart disease and carditis (as defined in the diagnostic criteria). Groups A and B contain all the cases without evidence of pre-existing heart disease at the time of admission. Group A includes: (1) cases with no carditis; (2) cases with murmurs of questionable significance (doubtful carditis); (3) cases with no, or doubtful, carditis but with a prolonged P–R interval. Group B includes cases with definite carditis at the start of therapy. Within both these groups, the number of cases with a definite previous history of rheumatic fever was negligible. Group C contains all those with definite or doubtful pre-existing rheumatic heart disease, whether or not carditis was also present. Both groups B and C are further subdivided into (1) cases with and (2) cases without pericarditis and/or failure at start of therapy.

Table 4 shows that the cases analysed in this way have in general fallen equally into the three treatment groups. The main departure lies in a somewhat lower number of cases on A.C.T.H. in group B (no pre-existing heart disease, carditis present at start of treatment). In the less important C group, in which the course of the disease is difficult to analyse because of pre-existing rheumatic heart disease, there is some predominance of cases with pericarditis and/or failure in the A.C.T.H. group.

TABLE 4.—*Condition of the Heart at Start of Therapy, by Duration from Onset. U.K. and U.S., all Cases*

Cardiac Group and Treatment Group	Total	Duration from Onset		
		0–14 Days	15–42 Days	43+ Days
Cardiac Group A—no or questionable carditis;* no pre-existing heart disease:				
A.C.T.H.	40	30	6	4
Cortisone	39	29	6	4
Aspirin	38	26	10	2
Total Group A	117	85	22	10
Cardiac Group B—carditis present; no pre-existing heart disease:				
A.C.T.H.	74	34	29	11
Cortisone	89	38	29	22
Aspirin	89	44	24	21
Total Group B	252	116	82	54
Cardiac Group C—with definite or questionable pre-existing heart disease:				
A.C.T.H.	48	22	12	14
Cortisone	39	18	10	11
Aspirin	41	14	12	15
Total Group C	128	54	34	40
Cases with failure and/or pericarditis included in Cardiac Group B:				
A.C.T.H.	13	4	6	3
Cortisone	14	3	7	4
Aspirin	10	7	—	3
Total	37	14	13	10
Cases with failure and/or pericarditis included in Cardiac Group C:				
A.C.T.H.	14	5	4	5
Cortisone	10	5	3	2
Aspirin	7	3	—	4
Total	31	13	7	11

* Questionable carditis includes 8 A.C.T.H., 6 cortisone, and 7 aspirin cases with a grade P murmur and 13 A.C.T.H., 12 cortisone, and 10 aspirin cases with a prolonged P–R interval and either no murmur or grade P murmur. (For definition of grade P murmur, see footnote to section on Murmurs.)

Returning to the incidence of the individual signs of involvement of the heart at start of therapy, Table 3 shows, for A.C.T.H., cortisone, and aspirin respectively, no appreciable differences for apical systolic murmurs (72.2%, 70.7%, and 66.1%), basal diastolic murmurs (25.3%, 23.4%, and 22.0%), and the proportion of cases with atrio-ventricular conduction time of 0.18 sec. or more (33.3%, 34.4%, and 28.3%). The proportions with a cardio-thoracic ratio of 0.55 or more were not equal, there being a smaller proportion in the aspirin group (22.0%, 18.5%, and 11.8%), but, as will be seen in the section on heart size (Table 20), this is largely due to the unequal distribution of cases with pre-existing heart disease (Group C). There was also a somewhat larger number of cases in failure at the start of therapy in the A.C.T.H. group, compared with the cortisone and aspirin groups (14.2%, 9.0%, and 6.0%).

Between the two countries, the individual signs of cardiac involvement were equally reported except for basal diastolic murmurs. These were more often reported in the U.K. (35.8%) than in the U.S. (12.1%), but this difference came from one U.K. centre only. Ninety-three of the 240 U.K. cases came from this centre, where the incidence of basal diastolic murmurs was 73.1%. In the remainder of the U.K. centres the incidence was 12.2%.

In short, these comparisons show that in many respects the three treatment groups were very similar—namely, in the duration-from-onset, age, sex, body weight, temperature, pulse during sleep, erythrocyte sedimentation rate, frequency of polyarthritis, subcutaneous nodules, erythema marginatum, and in the P–R interval. There are, however, a few differences. The group on aspirin included an undue proportion with chorea as a presenting symptom, although the few severe cases of chorea fell fairly equally in the three treatment groups. The A.C.T.H. group contained a larger proportion of cases with pericarditis and/or failure (particularly in the U.S.), and the aspirin group contained rather fewer (particularly in the U.K.). These differences are not large, but must be borne in mind in the study of the response of the illness to the different treatments.

Results

The course of rheumatic fever was followed in each case after admission to the study during the six-weeks period of treatment, three-weeks period of observation, at monthly intervals for six months following the end of the observation period, and at two-months intervals until the end of the first year (quarterly thereafter). This report includes an analysis of each symptom, sign, and laboratory test considered as evidence of active rheumatic fever or of rheumatic heart disease through a period of one year following the end of the observation period.

Each manifestation is considered at specified points of time and discussed individually. The methods of analysis include: comparison of averages; the proportion with a change greater than an arbitrary maximum amount; the proportion with a manifestation present or absent; the number, or percentage, above or below an arbitrary limit of normal. (With this last method of analysis, a constant number or percentage over a period of time does not indicate that the same cases continue abnormal but that of all the cases at risk the number abnormal remains the same.) In general, when several such indices yielded the same results, the simplest is reported; when two methods yielded differing results, both are reported. When a difference between treatment groups in one of these measurements is significant the probability value is reported; otherwise differences in results between treatments are not significant.

Temperature

Temperatures were measured four times a day throughout the nine-weeks period of treatment and observation. The maximum reading for each day is used in this analysis,

and cases are considered febrile if that reading (rectal) was 100.4° F. (38° C.) or above. The three groups were comparable on the day before treatment (Chart I). Following start of treatment, the proportion of febrile cases decreased rapidly in all three groups, although it was most rapid on the first day in the aspirin group (Chart I, Table 5). During the latter part of the first week the proportion febrile in the A.C.T.H. group was lower than that of the other two groups, but at the end of the week all three groups were in the same range, the aspirin group lagging slightly behind. In the main this lag in the aspirin group persisted throughout the six-weeks period of treatment, and was more prominent among the cases febrile than among those afebrile at start of treatment.

At the end of the sixth week of treatment there was a rise in the proportion of febrile cases in the A.C.T.H. group, persisting into the eighth week and then slowly decreasing. A similar rise occurred in the cortisone group, beginning in the seventh week, reaching a peak in the eighth, and decreasing slowly during the ninth week. The aspirin group showed a smaller rise with its peak in the seventh week, and decreasing during the eighth and ninth weeks. At the end of the ninth week all three groups had about the same proportion of febrile and afebrile cases (Table 6).

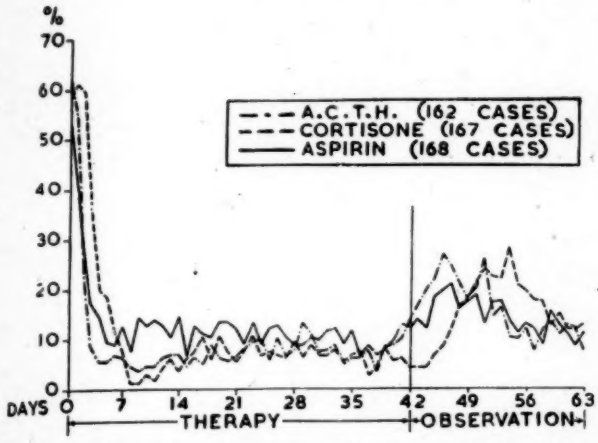

CHART I.—Temperature. Percentage of cases on each day with a rectal temperature of 100.4° F. (38° C.) or above.

TABLE 5.—*Temperature: Percentage of Cases with a Rectal Temperature of 100.4° F. (38° C.) or Above at Specified Times.* U.K. and U.S., all Cases*

Treatment Group	No. of Cases	Start of Therapy	Week of Therapy 1	2	3	4	5	6	Week of Observation 7	8	9
All Cases											
A.C.T.H.	162	53·7	5·8	6·0	6·6	8·9	5·8	13·4	19·3	9·7	9·6
Cortisone	167	61·1	6·8	5·2	6·8	7·0	6·4	4·8	18·2	19·1	12·2
Aspirin	168	40·5	9·7	10·3	11·3	9·1	8·9	12·8	17·0	11·9	9·5
Febrile Cases at Start of Treatment											
A.C.T.H.	87	100·0	5·8	7·7	6·9	10·0	6·5	14·1	21·8	9·6	6·7
Cortisone	102	100·0	6·5	6·2	7·0	7·6	5·6	4·3	20·6	20·9	12·0
Aspirin	68	100·0	12·7	15·7	16·7	14·3	8·3	13·7	20·2	13·6	12·5
Afebrile Cases at Start of Treatment											
A.C.T.H.	75	0·0	5·8	4·0	6·2	7·6	4·9	12·5	16·4	9·9	12·9
Cortisone	65	0·0	7·3	3·6	6·7	6·2	7·7	5·6	14·5	16·4	12·5
Aspirin	100	0·0	7·7	6·7	7·7	5·7	9·4	12·1	14·9	10·7	7·4

* To reduce irregularities, the values given for the end of the weeks are based upon all the observations made on *three* days centred at the end of the week—i.e., 6, 7, and 8 for week 1; 13, 14, and 15 for week 2; and so on up to days 62 and 63 for week 9.

TABLE 6.—*Temperature: Distribution at End of Ninth Week. U.K. and U.S., all Cases*

Rectal Temperature	No. with given Temperature at the End of the Ninth Week: A.C.T.H.	Cortisone	Aspirin
97·4° F. (36·3° C.)–	3	4	5
98·4° F. (36·9° C.)–	33	47	41
99·4° F. (37·4° C.)–	104	92	101
100·4° F. (38·0° C.)–	18	18	12
101·4° F. (38·6° C.)+	1	1	1
Not stated	3	5	8
Total	162	167	168

Pulse Rate During Sleep

The pulse rate was taken during sleep, between the hours of 12 midnight and 5 a.m. At start of treatment (Table 7), 31% to 36% of the patients in each group had a pulse rate of 100 per minute or more (tachycardia), while less than 5% had a rate of less than 60 per minute (bradycardia).

TABLE 7.—*Pulse Rate During Sleep: Percentage of Cases with Bradycardia (under 60) and Tachycardia (100 and over) at Specified Times.* U.K. and U.S., all Cases*

Treatment Group	No. of Cases	Start of Therapy	Week of Therapy 1	2	3	4	5	6	Week of Observation 7	8	9
Percentage with Bradycardia											
A.C.T.H.	162	4·6	14·7	10·9	7·4	6·1	3·8	2·5	0·0	0·6	0·7
Cortisone	167	2·0	18·3	24·7	13·7	12·0	8·3	6·9	2·0	0·4	0·3
Aspirin	168	4·1	4·8	10·0	9·3	7·1	4·3	1·6	3·8	1·5	4·3
Percentage with Tachycardia											
A.C.T.H.	162	35·8	13·9	10·7	9·6	13·9	12·7	13·3	24·6	21·4	21·3
Cortisone	167	34·6	10·1	6·5	7·2	7·5	6·3	5·9	13·2	22·7	20·1
Aspirin	168	30·6	10·1	7·9	6·9	7·3	5·3	6·8	10·7	8·8	6·7

* See footnote to Table 5.

Following start of treatment there was a slight rise in the proportion with tachycardia among the cortisone cases during the first two days. Apart from this, the proportion decreased at approximately the same rate in all three groups, reaching the same level in cortisone and aspirin at the end of the first week, the A.C.T.H. group having a slightly higher figure. These relative proportions remained unchanged throughout the treatment period. When therapy was stopped there was a sharp rise in the A.C.T.H. group and a slower rise to the same level in the cortisone group. At the end of the observation period one-fifth of the cases in both groups still had tachycardia. On the other hand, the proportion with tachycardia in the aspirin group remained almost unchanged when treatment ended and throughout the observation period (Table 7 and Chart II).

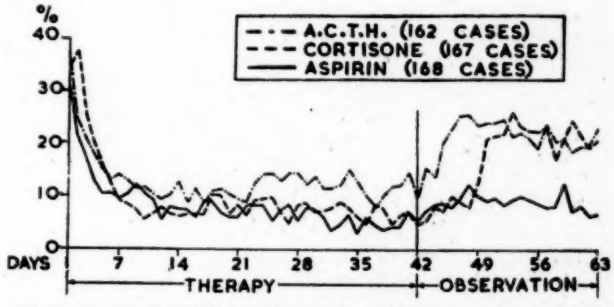

CHART II.—Tachycardia. Percentage of cases on each day with a pulse rate of 100 or more.

Detailed analysis showed that in all treatment groups there was the same rapid fall in the proportion with tachycardia among the cases of short duration (0–14 days), while in those of longer duration (15+ days) it fell more slowly. Thus, starting from the same level of 30% to 40% with tachycardia, there was a fall at the end of the first week to only 1% to 8% among the cases of short duration, in comparison with 13% to 22% among those of longer duration. This latter group lagged behind until the fourth or fifth week.

TABLE 8.—*Erythrocyte Sedimentation Rate: Percentage of Cases with a Rate of 20 mm./hour or higher (uncorrected) at Specified Times,* U.K. and U.S., all Cases.*

Treatment Group	No. of Cases	Start of Therapy	Week of Therapy						Week of Observation			Follow-up	
			1	2	3	4	5	6	7	8	9	13 Wks.	1 Year
A.C.T.H. ..	162	91·9	64·3	28·1	17·1	20·3	22·8	20·6	47·2	43·0	32·2	11·6	10·3
Cortisone ..	167	90·0	87·3	46·1	38·8	28·2	23·0	19·1	24·8	44·1	41·8	16·1	12·8
Aspirin	168	91·5	79·0	66·7	49·4	39·6	32·9	22·0	24·8	23·6	21·4	13·5	12·8

* The observations were not always made on the final day of the week, but were in most cases made at weekly intervals. A margin of ±3 days was allowed in deriving weekly values.

The proportion with bradycardia increased sharply after the start of treatment in both hormone groups, reaching 14.7% in the A.C.T.H. group at the end of the first week and almost 25% in the cortisone group at the end of the second week. From this point the proportion with bradycardia decreased to approximately the starting level by the end of the treatment period. In contrast, bradycardia occurred later in the aspirin group, reaching a peak of a little over 10% in the second to third weeks, and declining thereafter (Table 7 and Chart III).

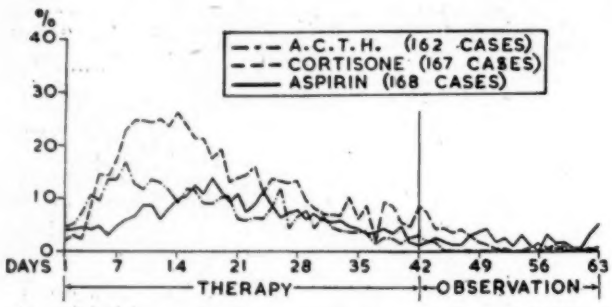

CHART III.—Bradycardia. Percentage of cases on each day with a pulse rate of 60 or less.

Erythrocyte Sedimentation Rate

The erythrocyte sedimentation rate was measured by the Wintrobe method (uncorrected)† at the start of treatment, weekly throughout the treatment and observation period, and at each follow-up examination. Its course was followed by tabulation of the proportion of cases with a rate of 20 mm. per hour at specified times.

At the start of treatment, approximately 90% of the cases in each treatment group had an elevated sedimentation rate. This proportion decreased rapidly in the hormone groups, with the A.C.T.H. group showing the sharpest drop, levelling off at the third week, in contrast to the cortisone group, which reached roughly this same level about the fifth week (Chart IV, Table 8). The proportion of those with an elevated rate in the aspirin group lagged distinctly behind that of both hormone groups, not reaching the same level until the last week of treatment. When treatment was stopped, however, there was a sharp rise in the proportion with a raised rate in the A.C.T.H. group, and a slower rise to the same level in the cortisone group, while there was no change in the aspirin group. By the 13th week the proportion in all three groups had reached the same low level of 12–16%. The very similar distribution of values at this point is shown in Table 9; at one year the proportions were relatively unchanged from the 13th-week figures. Separate analysis showed that these trends were the same for all three duration-from-onset groups.

†A corrected sedimentation rate of 15 mm./hr. or above was established as a minor diagnostic criterion for admission to the study, and was so used. In analysing the course of the disease for the first 13 weeks, an uncorrected rate of 20 mm./hr. or above was used, because (1) the centrifuges used in the haematocrit determinations were not standardized, with resulting variations from centre to centre, and (2) analysis of uncorrected and corrected readings for each of the drugs showed the same trends, and it seemed undesirable to introduce an unnecessary variable.

To summarize, during treatment the proportion with an elevated sedimentation rate decreased much more rapidly in the hormone groups than in the aspirin group, but it increased sharply, though temporarily, in both hormone groups after treatment was stopped, in contrast to a negligible change in the aspirin group. It finally reached the same low level in all three groups at 13 weeks, and this equal level was maintained at one year.

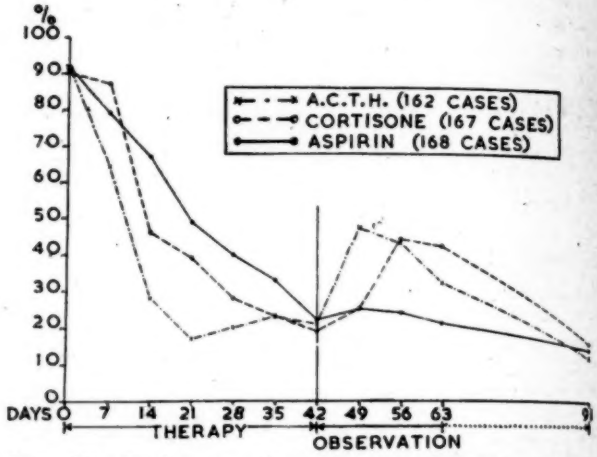

CHART IV.—Erythrocyte sedimentation rate. Percentage of cases with a rate of 20 mm./hr. or above (uncorrected Wintrobe).

TABLE 9.—*Erythrocyte Sedimentation Rate: Distribution at 13 Weeks. U.K. and U.S., all Cases*

Erythrocyte Sedimentation Rate (mm./hr. Uncorrected)	No. with Given Rate at 13 Weeks		
	A.C.T.H.	Cortisone	Aspirin
0–19	137	130	134
20–29	13	20	14
30–39	2	4	3
40–49	3	1	2
50–59	—	—	2
Not stated	7	12	13
Total	162	167	168

Joint Involvement‡

At start of therapy there was a greater proportion of cases with joint involvement in the U.S. centres (49.4%) than in the U.K. (36.7%), the difference occurring entirely among the early cases (Table 10). In both countries the percentages were about the same in each treatment group.

In each treatment group, cases with joint involvement on admission rapidly lost this symptom. Thus on the third day of therapy joint involvement was still present in 28.6% of A.C.T.H., 56.4% of cortisone, and 36.5% of aspirin cases.

‡Polyarthritis as a major manifestation for diagnosis of rheumatic fever was defined as "pain and either limitation of active motion, or tenderness in two or more joints." For following the course of this manifestation after start of treatment, a system of grading was adopted in which the lowest grade was defined as joint pain without objective joint findings. Since this lowest grade is less than that required for the definition of polyarthritis, the course of the manifestation is referred to as "joint involvement."

TABLE 10.—*Joint Involvement: Comparison of U.K. and U.S. Cases at Start of Therapy*

Duration from Onset at Start of Therapy (in Days)	U.K.			U.S.		
	Total Cases	With Joint Involvement		Total Cases	With Joint Involvement	
		No.	%		No.	%
0–14	109	57	52·3	146	101	69·2
15–42	79	20	25·3	59	13	22·0
43+	52	11	21·2	52	13	25·0
Total	240	88	36·7	257	127	49·4

By the eighth day it remained in less than 10% in each treatment group. Throughout the rest of the treatment period joint involvement was present in none of the cortisone cases, in only a rare case in the A.C.T.H. group, and in a few cases in the aspirin group (Table 11). After treatment was stopped there was an insignificant increase of cases with joint involvement in the A.C.T.H. group, and these had disappeared by the 13th week; in the cortisone group there was an immediate rise to 10.3%, followed by complete disappearance at the ninth week and one recurrence at the 13th week: in the aspirin group two cases continued up to the 13th week. Among cases in which joint involvement disappeared it later reappeared in only a few cases (A.C.T.H. 5, cortisone 15, and aspirin 8).

TABLE 11.—*Cases with Joint Involvement at Start of Therapy: Number and Percentage with Joint Involvement at Specified Times. U.K. and U.S., all Cases*

Time from Start of Therapy	A.C.T.H.		Cortisone		Aspirin	
	No. of Cases	%	No. of Cases	%	No. of Cases	%
1 day	63	100·0	78	100·0	74	100·0
2 days	41	65·1	59	75·6	52	70·3
3 ,,	18	28·6	44	56·4	27	36·5
4 ,,	12	19·0	27	34·6	11	14·9
5 ,,	5	7·9	17	21·8	9	12·2
6 ,,	7	11·1	13	16·7	9	12·2
7 ,,	5	7·9	8	10·3	9	12·2
8 ,,	4	6·3	6	7·7	6	8·1
15 ,,	1	1·6	—	0·0	6	8·1
22 ,,	2	3·2	—	0·0	5	6·8
29 ,,	1	1·6	—	0·0	6	8·1
36 ,,	2	3·2	—	0·0	2	2·7
43 ,,	2	3·2	—	0·0	4	5·4
50 ,,	3	4·8	8	10·3	6	8·1
57 ,,	2	3·2	7	9·0	5	6·8
63 ,,	1	1·6	—	0·0	2	2·7
13th week	—	0·0	1	1·3	2	2·7

TABLE 12.—*Cases without Joint Involvement at Start of Therapy: Development of Joint Involvement During Specified Intervals. U.K. and U.S., all Cases*

Treatment Group	No. of Cases Without Joint Involvement at Start of Therapy	No. Developing Joint Involvement		
		1–42 Days	43–63 Days	At 13 Weeks
A.C.T.H.	99	4	5	—
Cortisone	89	5	4	—
Aspirin	94	—	4	—

Among cases *without* joint involvement at start of therapy (Table 12), a few developed it during the 13-weeks period (A.C.T.H. 9, cortisone 9, aspirin 4). In five A.C.T.H., four cortisone, and the four aspirin cases the joint involvement appeared for the first time after the end of treatment.

There is little to choose between the three drugs in their effect on joint involvement, apart from some delay in response to cortisone administered intramuscularly.

Chorea

At the start of therapy there was a larger proportion of cases with chorea in the aspirin group than in either of the hormone groups. Chorea seemed to persist longer in the aspirin than in the hormone groups, but this difference is not significant (Table 13). The persistence of this symptom was strikingly more pronounced in the U.K. than in the U.S. cases, since at 13 weeks nearly all were in U.K. centres (the A.C.T.H. case, one of three cortisone, and eight of nine aspirin cases).

Among the cases *without* chorea at the start of therapy, a few in all three treatment groups developed this symptom at some time during the 13-weeks period (Table 14).

The persistence of chorea, as well as its appearance for the first time, was not significantly different between the treatment groups.

TABLE 13.—*Cases with Chorea at Start of Therapy: Subsequent Course. U.K. and U.S., all Cases*

Treatment Group	No. of Cases with Chorea at Start of Therapy	No. with Chorea at		
		End of Therapy (Week 6)	End of Observation (Week 9)	Follow-up (13 Weeks)
A.C.T.H.	9	1	—	1
Cortisone	19	2	1	3
Aspirin	26	9	5	9

TABLE 14.—*Cases without Chorea at Start of Therapy: Development of Chorea During Specified Time Intervals. U.K. and U.S., all Cases*

Treatment Group	No. of Cases Without Chorea at Start of Therapy	No. Developing Chorea		
		1–42 Days	43–63 Days	At 13 Weeks
A.C.T.H.	153	3	—	—
Cortisone	148	3	—	2
Aspirin	142	4	—	1

Subcutaneous Nodules

At the start of therapy there was a significantly larger proportion of cases with subcutaneous nodules in the U.K. (21.7%) than in the U.S. (7.4%), most of the difference occurring in the group of late cases (Table 15). Among the three treatment groups in the two countries, however, such cases were fairly evenly distributed except for slightly fewer in the aspirin group.

TABLE 15.—*Nodules: Comparison of U.K. and U.S. Cases at Start of Therapy*

Duration from Onset at Start of Therapy (in Days)	U.K.			U.S.		
	Total Cases	With Nodules		Total Cases	With Nodules	
		No.	%		No.	%
0–14	109	6	5·5	146	2	1·4
15–42	79	14	17·7	59	7	11·9
43+	52	32	61·5	52	10	19·2
Total	240	52	21·7	257	19	7·4

In most of the early and medium-duration cases (0–42 days) receiving A.C.T.H. or cortisone, subcutaneous nodules had disappeared by the end of treatment (Table 16). In the aspirin group, although the number with nodules was fairly small, the nodules tended to persist to the end of the sixth week. This tendency was even more apparent among the chronic cases (43+ days), although the rate of disappearance in these cases was perhaps lower with all three drugs. These differences in response came from the U.K. cases, since at the end of six weeks only two, and at 13 weeks only one, with nodules still remaining were U.S. cases.

New subcutaneous nodules developed in some cases during the treatment period in all treatment groups, and particularly among cases with nodules at the start of therapy (Tables 16 and 17). During the treatment period there was a slightly greater tendency for cases in the aspirin group to develop new nodules than among those in the hormone groups. Of the 36 cases in all treatment groups in which new nodules developed during therapy, 25 were U.K. cases.

Thus it may be concluded that new nodules appeared on all treatments and that nodules persisted longer in the aspirin- than in the A.C.T.H.- and cortisone-treated cases.

TABLE 16.—*Cases with Nodules at Start of Therapy: Subsequent Course. U.K. and U.S., all Cases*

Treatment Group and Duration from Onset	No. with Nodules at Start of Therapy	No. with Nodules Persisting to: End of Therapy (Week 6)	End of Observation (Week 9)	Follow-up (13 Weeks)
0–42 days:				
A.C.T.H. ..	13	4	1	—
Cortisone ..	12	4	2	1
Aspirin ..	4	3	2	1
43 days+:				
A.C.T.H. ..	13	6	4	3
Cortisone ..	13	7	4	1
Aspirin ..	16	12	12	10

		No. in which *Fresh* Nodules Appeared: 1–42 Days	43–63 Days	At 13th Week
All duration groups:				
A.C.T.H. ..	26	5	2	1
Cortisone ..	25	3	—	—
Aspirin ..	20	9	2	1

TABLE 17.—*Cases without Nodules at Start of Therapy: Development of Nodules During Specified Time Intervals. U.K. and U.S., all Cases*

Treatment Group	No. of Cases Without Nodules at Start of Therapy	No. Developing Nodules: 1–42 Days	43–63 Days	At 13 Weeks
A.C.T.H. ..	136	7	—	1
Cortisone ..	142	2	—	—
Aspirin ..	148	10	1	1

Erythema Marginatum

At the start of therapy there were 29 cases with erythema marginatum (A.C.T.H. 12, cortisone 11, aspirin 6). The proportion with new episodes developing during treatment and observation was similar for all treatment groups (Table 18). At 13 weeks, erythema marginatum had persisted in two A.C.T.H. cases and one aspirin case.

Among the cases *without* erythema marginatum at start of treatment, the number developing episodes for the first time during treatment or observation was also similar for all treatment groups (A.C.T.H. 10, cortisone 15, and aspirin 11). Among these cases only one remained at 13 weeks—a cortisone case which first manifested erythema marginatum during the observation period. In addition there was one aspirin case in which erythema marginatum appeared for the first time at the 13th week (Table 19).

Thus the rate of appearance or disappearance of episodes of erythema marginatum seemed to be unrelated to therapy.

TABLE 18.—*Cases with Erythema Marginatum at Start of Therapy: New Episodes of Erythema Marginatum. U.K. and U.S., all Cases*

Treatment Group	No. of Cases with Erythema Marginatum at Start of Therapy	New Episodes Developing: 1–42 Days	43–63 Days	At 13 Weeks
A.C.T.H. ..	12	5	1	—
Cortisone ..	11	2	2	—
Aspirin ..	6	2	1	—

TABLE 19.—*Cases without Erythema Marginatum at Start of Therapy: Development of Erythema Marginatum During Specified Time Intervals. U.K. and U.S., all Cases*

Treatment Group	No. of Cases without Erythema Marginatum at Start of Therapy	No. Developing Erythema Marginatum: 1–42 Days	43–63 Days	At 13 Weeks
A.C.T.H. ..	150	9	1	—
Cortisone ..	156	10	5	—
Aspirin ..	162	9	1	1

Heart Size

Variations in heart size were analysed by three methods:

1. The proportion in each treatment group with a cardiothoracic ratio of 0.55 or more; this method described extreme grades of cardiac enlargement.

2. The frequency of change in transverse cardiac diameter of 0.6 cm. or more, between 0–3, and 3–6, and 6–9 weeks and 0–1 year; this method, although starting from an abnormal base line, was more sensitive than method 1 to temporary changes of a lesser degree.

3. The proportion of cases with a cardiothoracic ratio of 0.50 or more; this method yielded no additional information and will not be further discussed.

In Cardiac Group A the proportion with a cardiothoracic ratio of 0.55 or more in any treatment group at any time was insignificant (Table 20). In Cardiac Group B (excluding those with failure or pericarditis or both) the approximately equal distribution among the three treatment groups persists throughout. In Cardiac Group C (excluding those with failure or pericarditis or both) there was a smaller proportion of cases initially in the aspirin group with extreme grades of cardiac enlargement. This inequality persists at three, six, and nine weeks, but disappears at one year. In the group of cases with failure or pericarditis or both, the relative inequality persists throughout.

Using the more sensitive index of change in heart size of 0.6 cm. or more, a larger proportion showed an increase over the 0–9 weeks period in each hormone compared with the aspirin group. This difference appeared early, since analysis of the 0–3 and 3–6 weeks intervals showed the same result, but at one year it had disappeared (Chart V). In contrast, the proportion showing a decrease in heart size was similar for all treatment groups. Cardiac groups A, B, and C all showed this difference between each of the hormones and aspirin early in treatment and the same equality at the end of one year. Among cases with failure and/or pericarditis (in which the proportion of enlarged hearts was

TABLE 20.—*Cardiothoracic Ratio: Percentage of Cases in Cardiac Groups with T.D./I.D. Ratio of 0.55 or More at Specified Times. U.K. and U.S., all Cases**

Cardiac Group and Treatment Group	No. of Cases	Start of Therapy	Week 3	End of Therapy Week 6	End of Observation Week 9	Follow-up One Year
Cardiac Group A: No or questionable carditis, no pre-existing heart disease:						
A.C.T.H.	40	2·6	0·0	0·0	2·7	2·9
Cortisone	39	2·7	2·9	0·0	0·0	0·0
Aspirin ..	38	0·0	0·0	0·0	0·0	0·0
Cardiac Group B†: Carditis present, no pre-existing heart disease:						
A.C.T.H.	61	5·0	8·3	12·1	8·6	10·2
Cortisone	75	10·7	7·1	10·3	8·4	6·0
Aspirin ..	79	9·2	13·9	6·4	7·8	5·8
Cardiac Group C†: With definite or questionable pre-existing heart disease:						
A.C.T.H.	34	27·3	30·3	28·1	29·0	13·8
Cortisone	29	29·6	28·6	31·0	37·0	17·4
Aspirin ..	34	15·2	15·2	15·2	9·4	16·0
Congestive failure and/or pericarditis:						
A.C.T.H. ..	27	81·5	66·7	68·0	64·0	47·8
Cortisone ..	24	56·5	50·0	52·2	31·8	19·0
Aspirin ..	17	43·8	58·8	41·2	31·2	27·3
All groups:						
A.C.T.H. ..	162	22·0	20·8	21·6	20·5	15·6
Cortisone ..	167	18·5	16·1	17·9	14·8	8·5
Aspirin ..	168	11·8	15·7	10·2	8·9	8·0

* At the specified times there were sometimes one or two observations missing. The percentages are based upon the numbers available.
† Excluding cases with failure and/or pericarditis at start of therapy.

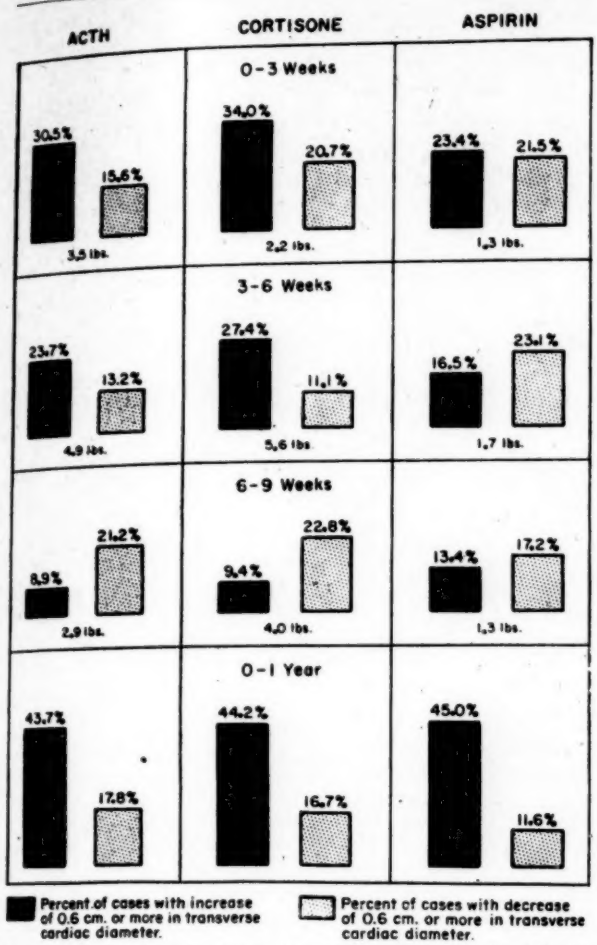

CHART V.—Changes in heart size and average weight gain in specified time intervals.

high at start of therapy), approximately one-third showed an early decrease regardless of therapy, and few (16%) showed an increase during treatment.

Considering gains in body weight, increases in heart size were more frequent in each hormone group than in the aspirin group during 0–3 and 3–6 weeks, but not during 6–9 weeks. In each period, however, both hormone groups had an average weight gain two to three times as great as the aspirin group; in other words, there was no clear relationship between weight gain and increase in heart size.

In summary, when heart size is measured by the proportion with a cardiothoracic ratio of 0.55 or more, the cardiac subgroups and the total cases reveal no differences between treatments. Using the more sensitive index of change in heart size of 0.6 cm. or more, there is a tendency for cases treated with A.C.T.H. or cortisone to show a temporary increase in heart size.

Atrioventricular Conduction Time

The course of the atrioventricular conduction time* (measured by the P–R interval in the electrocardiogram) was analysed, using:

1. The percentage with a P–R interval of 0.18 sec. or longer.
2. The percentage with a P–R interval of 0.16 sec. or longer.
3. The average P–R interval.
4. The percentage with an increase or decrease in the P–R interval of 0.03 sec. or more during the interval of 0–3, 0–6, 6–9, and 0–9 weeks.

The four methods led to the same conclusions, and only the percentages with a P–R interval of 0.18 second or longer are presented here.

The proportions of cases with a P–R interval of 0.18 second or longer are distributed fairly equally at start of therapy in each of the treatment and each of the cardiac groups (Chart VI, Table 21). They decreased initially more

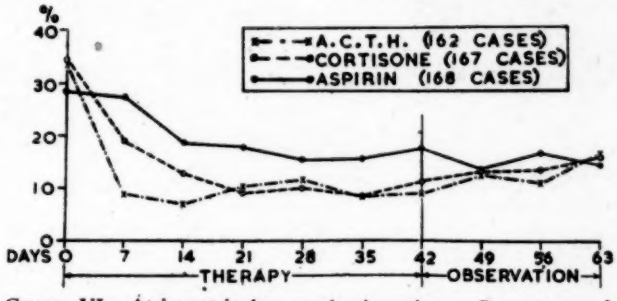

CHART VI.—Atrioventricular conduction time. Percentage of cases with P–R interval of 0.18 second or more.

TABLE 21.—*Atrioventricular Conduction Time: Percentage of Cases in Cardiac Groups with P–R Interval of 0.18 sec. or Above at Specified Times. U.K. and U.S., all Cases**

Cardiac Group and Treatment Group	No. of Cases	Start of Therapy	Week 3	End of Therapy Week 6	End of Observation Week 9	Follow-up One Year
Cardiac Group A: No or questionable carditis, no pre-existing heart disease:						
A.C.T.H.	40	36·8	5·3	5·7	7·1	6·5
Cortisone	39	40·5	8·1	11·1	13·6	18·5
Aspirin ..	38	30·6	13·3	15·2	20·0	0·0
Cardiac Group B†: Carditis present, no pre-existing heart disease:						
A.C.T.H.	74	28·2	6·1	6·0	14·3	14·3
Cortisone	89	29·3	7·3	11·4	12·7	22·5
Aspirin ..	89	25·6	14·5	13·8	10·0	12·3
Cardiac Group C†: With definite or questionable pre-existing heart disease:						
A.C.T.H.	48	38·3	20·5	15·9	25·6	30·8
Cortisone	39	40·0	13·9	10·8	24·2	11·1
Aspirin ..	41	32·4	28·2	27·5	20·0	25·9
All groups:						
A.C.T.H. ..	162	33·3	10·1	8·9	16·4	17·5
Cortisone ..	167	34·4	9·0	11·2	15·9	19·2
Aspirin ..	168	28·3	17·8	17·6	14·4	12·5

* See footnote to Table 20.
† Includes cases with failure and/or pericarditis at start of therapy.

rapidly among those receiving A.C.T.H. or cortisone than among those receiving aspirin, with the A.C.T.H. group showing a very rapid fall at the end of the first week from 33.3% to 8.7% and in the second week to 6.9%. At the third week the A.C.T.H. and cortisone groups were at the same level, with the aspirin group clearly lagging behind. This difference was maintained to the end of the treatment period, after which, at 9 weeks and at one year, all three groups were in the same range (13% to 19%). This decrease during treatment in the hormone-treated cases occurred in all cardiac groups, but was less marked in cardiac group C.

The hormones appear to decrease the P–R interval to values below those at 9 weeks and at one year. The values at these later times might well be expected to be closer to normal than those recorded during the acute illness. It may be questioned, therefore, whether the early decrease in P–R intervals is an effect of the hormones on the disease or merely a direct effect on the atrioventricular conduction time.

*The diagnostic criteria for admission of patients to the study defined normal P–R intervals as corrected for age and heart rate according to the Ashman–Hull tables. These corrections were not used in evaluating the course of the disease because the P–R intervals were unduly influenced by marked pulse rate changes, and because recent unpublished studies of the P–R interval in normal children by the Child Research Council of Denver question the corrections proposed by Ashman and Hull.

TABLE 23.—*Cardiac Group B* (with carditis, no pre-existing heart disease): Apical Systolic Murmurs, Grades at Start of Therapy and at Specified Times. U.K. and U.S., all Cases*

Grade at Start of Therapy and Treatment Group	Total Cases	Grade at end of Therapy (Week 6)				Grade at end of Observation (Week 9)				Grade at Follow-up (13 Weeks)					Grade at Follow-up (One Year)				
		0	1	2	3	0	1	2	3	0	1	2	3	Not Known	0	1	2	3	Not Known
Grade O:																			
A.C.T.H. ..	5	4	–	1	–	4	–	1	–	4	–	1	–	–	5	–	–	–	–
Cortisone ..	8	8	–	–	–	8	–	–	–	7	–	–	–	1	7	–	–	–	1
Aspirin ..	12	10	2	–	–	11	1	–	–	11	–	–	–	1	11	–	–	–	1
Grade 1:																			
A.C.T.H. ..	14	10	2	1	1	11	2	–	1	11	2	1	–	–	12	1	1	–	–
Cortisone ..	27	19	7	1	–	14	11	1	1	20	5	–	2	–	17	7	3	–	–
Aspirin ..	18	4	10	4	–	6	8	4	–	7	7	3	–	1	10	5	3	–	–
Grade 2:																			
A.C.T.H. ..	35	9	9	15	2	7	11	15	2	6	11	14	3	1	10	9	10	3	3†
Cortisone ..	36	8	14	14	–	11	12	13	–	12	13	10	1	–	19	7	7	2	1
Aspirin ..	49	5	17	24	3	12	13	19	5	10	14	18	5	2	24	9	9	6	1†
Grade 3:																			
A.C.T.H. ..	20	1	3	9	7	1	2	8	9	3	1	8	8	–	4	3	6	7	–
Cortisone ..	16	1	–	6	9	–	1	6	9	–	3	3	9	1	2	2	2	9	1
Aspirin ..	10	–	2	3	5	1	1	4	4	1	2	4	3	–	2	1	5	1	1
Grade not Stated:																			
Cortisone ..	2	1	–	–	1	1	–	1	–	1	–	1	–	–	1	–	–	1	–

*Includes cases with failure and/or pericarditis at start of therapy. †Includes one death.

Apical Systolic and Basal Diastolic Murmurs‡

The development and course of significant heart murmurs are among the most important aspects of rheumatic fever. They are analysed during the acute attack (0–13 weeks) and at one year, according to the status of the heart at the start of treatment—that is, Cardiac Group A, those without pre-existing heart disease or carditis; Cardiac Group B, those with carditis and without pre-existing heart disease; and Cardiac Group C, those with pre-existing heart disease.

Cardiac Group A

Each treatment group included approximately the same number of cases without carditis or pre-existing heart disease. None of these had an apical systolic or basal diastolic murmur on admission to the study. During the nine-weeks period of treatment and observation it was unusual for either of these murmurs to appear, and at 13 weeks few cases had either an apical systolic or a basal diastolic murmur or both, regardless of the type of therapy (Table 22). At 13 weeks,

TABLE 22.—*Cardiac Group A (no Carditis, no Pre-existing Heart Disease): Murmurs Present at Specified Times. U.K. and U.S., all Cases*

	Total Cases	No. with Murmurs at			
		End of Therapy (Week 6)	End of Observation (Week 9)	Follow-up (13 Weeks)	Follow-up One Year
A.C.T.H. ..	40	3	5	5	5
Cortisone ..	39	2	1	3	4
Aspirin	38	3	2	2	5

among 40 A.C.T.H. cases there were five with apical systolic murmurs; among 39 cortisone cases there was one with an apical systolic murmur, one with a basal diastolic murmur, and one with both; and among the 38 aspirin cases there were two with apical systolic murmurs. At one year apical systolic murmurs were still few: five A.C.T.H., four cortisone, and five aspirin. One of the cortisone cases also had a basal diastolic murmur. In other words, if a case of rheumatic fever meeting the criteria for admission to this study had no apical systolic or basal diastolic murmur at that time the chance of developing either murmur during the acute attack or at one year was only approximately 1 in 8, regardless of treatment.

Cardiac Group B

Among the cases with carditis without pre-existing heart disease, the distribution of apical systolic murmurs by grades was not the same in the three treatment groups at start of therapy; there were relatively more Grade O and Grade 2 murmurs among the aspirin, Grade 1 among the cortisone, and Grade 3 among the A.C.T.H. cases. For this reason, analysis of the group as a whole becomes complicated and each grade is analysed separately.

The Group B cases without an apical systolic murmur at start of therapy (included in Group B on account of other murmurs, increase in heart size, failure or pericarditis) behaved much like the cases without carditis (Group A). It was unusual for them to develop an apical systolic murmur during the first 13 weeks following the start of treatment or at one year, regardless of the treatment employed (Table 23).

In Group B cases, Grade 1 apical systolic murmurs at start of treatment appeared to respond differently during the acute attack in hormone-treated cases compared with the aspirin-treated cases. In the majority of the cases treated with A.C.T.H. or cortisone the Grade 1 murmur disappeared by the end of six weeks of treatment. There was a slight increase in their frequency among the cortisone cases at nine weeks, but otherwise there was no appreciable change at the 9th and 13th weeks. By contrast, in only 4 of 18 aspirin cases did the Grade 1 apical systolic murmur disappear at six weeks and in only seven by the 13th week. There were relatively few Grade 1 murmurs that increased to Grade 2 or 3 during the 13-weeks period in any of the treatment groups. At one year following the end of the observation period, the differences between the three treatment groups were no longer significant (Table 23).

Grade 2 apical systolic murmurs in cases with carditis (Group B) presented a somewhat different pattern. These murmurs disappeared in slightly more cortisone than A.C.T.H. or aspirin cases. Thus by the end of 13 weeks they had disappeared in about one-sixth of the A.C.T.H., one-fifth of the aspirin, and one-third of the cortisone cases. Considering murmurs which decreased as well as those which disappeared, the differences among the treatment groups are not so great. At the end of 13 weeks in one-half of the A.C.T.H. and aspirin cases the Grade 2 murmur had diminished or had disappeared, in comparison with five-sevenths of the cortisone cases. With the number of cases studied, none of these differences reached the 5% level of

‡In this study the following grades were adopted for reporting apical systolic murmurs: Grade O—No murmur, or a murmur considered to be "functional" on the basis of its apparent origin at the pulmonic area or along the left sternal border. Grade P—Murmur apparently localized to the apical area, but so faint as not to be transmitted to or toward the axilla. Grade 1—Soft apical systolic murmur transmitted to or toward the axilla. Grade 2—Louder similar murmur. Grade 3—Very loud similar murmur, usually transmitted to the back. In the analysis of the data, the "P" murmurs were included under Grade O.

significance. By the end of one year, only minor differences remained. Thus in the Group B cases there were no striking differences in the effect of A.C.T.H., cortisone, or aspirin on Grade 2 apical systolic murmurs during the acute attack or at one year.

Grade 3 apical systolic murmurs in cases with carditis did not disappear, except in a few instances, during the 13-weeks period or at one year, regardless of the type of treatment (Table 23). Some of these loud murmurs became less intense, particularly in the aspirin group, but this difference again was not significant.

Summarizing, the apical systolic murmurs in Group B cases responded in relatively the same way to the three forms of treatment, except when the apical systolic murmur was of minimum intensity (Grade 1). In these cases a larger proportion of such murmurs disappeared during therapy with A.C.T.H. and cortisone than with aspirin, but there was little difference between treatment groups at the end of one year.

In 11 centres, basal diastolic murmurs in cardiac Group B cases were recorded in 20 of 201 (10%), while in one U.K. centre they were present in 41 cases (80%), absent in 8, and undetermined in 2. Two separate analyses are therefore presented.

In the 11 centres, basal diastolic murmurs were present at the start of therapy in 7 of 58 A.C.T.H., 8 of 70 cortisone, and 5 of 73 aspirin cases (Table 24). At 6, 9, 13 weeks, and one year the disappearance of these murmurs or their appearance in cases originally without them was approximately the same for all treatment groups.

In the one U.K. centre, of eight cases initially without basal diastolic murmurs one developed a transient murmur. In 41 cases where the murmur was initially present it had disappeared by nine weeks more frequently from the A.C.T.H. (14 of 15) than from the cortisone (6 of 13) and aspirin groups (4 of 13). The difference was still present at one year (13 of 15 A.C.T.H., 4 of 12 cortisone, and 5 of 12 aspirin).

Cardiac Group C

These cases with pre-existing heart disease, including those with additional pericarditis or failure or both on admission, are difficult to evaluate.

The disappearance of apical systolic murmurs Grades 1 and 2 during the acute attack was slower in the aspirin group: in 8 of 32 A.C.T.H. and 8 of 23 cortisone cases these murmurs had disappeared at the end of 13 weeks, as compared with 2 of 23 cases in the aspirin group (Table 25). However, at one year there was very little difference between the three treatment groups. None of the 43 Grade 3 apical systolic murmurs had disappeared at 13 weeks after start of therapy, and only two (1 A.C.T.H. and 1 cortisone) had disappeared by the end of one year.

In the Group C cases from 11 centres, the appearance or disappearance of basal diastolic murmurs showed no differences among the treatment groups during the acute attack or at one year (Table 26). A few new basal diastolic murmurs appeared, and an insignificant number of those present disappeared during the 13-weeks period or at one year. In the one U.K. centre, separately considered, there were also no differences between treatment groups. Only 2 of 29 Group C cases had no basal diastolic murmurs initially and none appeared later. Where the murmur was present initially, it persisted to one year in 7 of 10 A.C.T.H., 6 of 6 cortisone, and 9 of 11 aspirin cases.

This analysis of apical systolic and basal diastolic murmurs among Group C cases showed only one difference—a more rapid disappearance of lower grades of apical systolic murmurs in cases receiving A.C.T.H. and cortisone.

Apical Diastolic Murmurs

Mid-diastolic Murmurs

This analysis of mid-diastolic murmurs is limited to the data for the U.K. centres, differing from the pattern of presentation elsewhere in this report. The U.S. data are not included, since a review of the records indicated that varying

TABLE 24.—*Cardiac Group B* (with carditis, no pre-existing heart disease): Basal Diastolic Murmurs at Start of Therapy and at Specified Times. U.K. and U.S. Cases†*

Status at Start of Therapy and Treatment Groups	Total Cases	End of Therapy (Week 6)		End of Observation (Week 9)		Follow-up (13 Weeks)			Follow-up (One Year)		
		Absent	Present	Absent	Present	Absent	Present	Not Known	Absent	Present	Not Known
No Murmur at Start:											
A.C.T.H.	51	48	3	49	2	48	2	1	48	1	2‡
Cortisone	62	60	2	60	2	59	2	1	58	3	1
Aspirin	68	63	5	64	4	63	2	3	62	4	2‡
Murmur Present at Start:											
A.C.T.H.	7	1	6	1	6	2	5	–	1	5	1
Cortisone	8	3	5	3	5	5	3	–	2	5	1
Aspirin	5	2	3	2	3	2	3	–	2	3	–

* Includes cases with failure and/or pericarditis at start of therapy.
† Includes 201 cases in 11 of the 12 centres where basal diastolic murmurs were present at start of therapy in 10% of cases, and excludes 51 cases in one centre where basal diastolic murmurs were present in 41 cases (80%), absent in 8, and undetermined in 2 because of a loud pericardial friction rub.
‡ Includes one death.

TABLE 25.—*Cardiac Group C§ (with definite or questionable pre-existing heart disease): Apical Systolic Murmurs, Grades at Start of Therapy and at Specified Times. U.K. and U.S., all Cases*

Grade at Start of Therapy and Treatment Group	Total Cases	Grade at End of Therapy (Week 6)				Grade at End of Observation (Week 9)				Grade at Follow-up (13 Weeks)					Grade at Follow-up (One Year)				
		0	1	2	3	0	1	2	3	0	1	2	3	Not Known	0	1	2	3	Not Known
Grade 0 at Start:																			
A.C.T.H.	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Cortisone	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Aspirin	7	5	1	1	–	4	2	1	–	4	1	–	–	2	6	1	–	–	–
Grades 1 & 2 at Start:																			
A.C.T.H.	32	5	8	16	3	7	6	15	4	8	3	15	5	1	7	9	12	4	–
Cortisone	23	4	8	11	–	5	8	10	–	8	5	10	–	–	6	7	9	1	–
Aspirin	23	1	2	19	1	2	5	15	1	2	3	15	3	–	6	3	13	–	1‖
Grade 3 at Start:																			
A.C.T.H.	16	–	–	2	14	–	–	3	13	–	1	2	13	–	1	–	3	11	1
Cortisone	16	1	–	5	10	–	1	4	11	–	1	4	10	1‖	1	–	5	8	2‖
Aspirin	11	–	–	4	7	–	–	5	6	–	–	5	6	–	–	1	5	4	1‖

§ Includes cases with failure and/or pericarditis at start of therapy. ‖Includes one death.

TABLE 26.—*Cardiac Group C* (with definite or questionable pre-existing heart disease): Basal Diastolic Murmurs at Start of Therapy and at Specified Times. U.K. and U.S. Cases†*

Status at Start of Therapy and Treatment Group	Total Cases	End of Therapy (Week 6)		End of Observation (Week 9)		Follow-up (13 Weeks)			Follow-up (One Year)		
		Absent	Present	Absent	Present	Absent	Present	Not Known	Absent	Present	Not Known
No Murmur at Start:											
A.C.T.H.	29	26	3	27	2	26	3	–	24	5	–
Cortisone	20	18	2	18	2	18	2	–	18	2	–
Aspirin	21	20	1	19	2	17	2	2	16	3	2‡
Murmur Present at Start:											
A.C.T.H.	9	1	8	3	6	2	7	–	2	6	1
Cortisone	12	1	11	1	11	–	11	1‡	1	10	1‡
Aspirin	8	1	7	1	7	1	7	–	2	6	–

* Includes cases with failure and/or pericarditis at start of therapy.
† Includes 99 cases in 11 of the 12 centres where basal diastolic murmurs were present at start of therapy in 29% of cases, and excludes 29 cases in one centre where basal diastolic murmurs were present in 93% of cases.
‡ Includes one death.

terms—namely, mid-diastolic murmur, third heart sound, and gallop rhythm—were recorded inconsistently from centre to centre and from observer to observer of the same case in the same centre. Further, in acute rheumatic carditis this murmur is rarely heard in the absence of an organic apical systolic murmur, which was consistently recorded. The U.S. investigators therefore agreed that the mid-diastolic murmur in the U.S. cases should not be analysed.

In the U.K. no such murmur developed during the year in Group A cases. In Group B, where the murmur was initially absent it appeared in only a few cases, equally in all treatment groups. Where it was initially present it persisted up to the 13th week to a greater extent in the aspirin group (9 of 17 cases) compared with A.C.T.H. (3 of 19) and cortisone (5 of 18). At one year, however, there was little difference between the three groups (1 of 17 A.C.T.H., 3 of 18 cortisone, and 3 of 16 aspirin). In Group C cases, where the murmur was initially absent it appeared in a few cases in all treatment groups by the end of one year. Where the murmur was initially present it persisted in all treatment groups at the ninth week (13 of 20 A.C.T.H., 12 of 19 cortisone, and 15 of 19 aspirin), becoming slightly less at one year (9, 10, 9 cases, respectively).

Presystolic Murmurs

Apical presystolic murmurs were not included in this analysis, as they result from slowly progressive scarring of the mitral valve and are not evidence of acute carditis. In this study they were present in only 16 of 497 cases (3.2%) on admission, and they appeared for the first time in very few (12 additional cases during the following 13 weeks).

Summary of Murmurs

Summarizing the effects of treatment on murmurs during the acute attack and at the end of the first year, the following conclusions appear justified :

1. The development of an apical systolic murmur among those without such murmurs at start of therapy, regardless of the presence or absence of carditis, was infrequent and was not related to the treatment.

2. The disappearance of softer apical systolic murmurs was more rapid among those receiving A.C.T.H. or cortisone than among those receiving aspirin, but at the end of one year the treatment groups did not differ significantly. Similar results were found for the apical mid-diastolic murmur for the U.K. centres only.

3. The disappearance or diminution of loud apical systolic murmurs rarely occurred, regardless of therapy.

4. The appearance or disappearance of basal diastolic murmurs occurred in a relatively small proportion of cases, and in 11 of 12 centres was not related to therapy.§

5. At the end of one year there was no evidence that the treatment groups differed in the frequency with which murmurs had appeared or disappeared.

§In the one U.K. centre where an abnormally high proportion of basal diastolic murmurs was heard at entry, they disappeared more frequently in the A.C.T.H. group.

Seriously Ill Cases

Cases here described as seriously ill are those with congestive failure, pericarditis, or both, present on admission or occurring during the 13-weeks period of treatment and follow-up, and those cases terminated by death during the one-year period of this report.

Congestive Failure and/or Pericarditis

At the start of treatment, 23 of 162 A.C.T.H., 15 of 167 cortisone, and 10 of 168 aspirin cases had congestive failure (Table 27). Among these cases, failure disappeared

TABLE 27.—*Congestive Failure: U.K. and U.S., all Cases*

Interval from Start of Therapy in Days	Cases with Failure at Start of Therapy			Cases without Failure at Start of Therapy		
	No. with Failure Present on First Day of Interval			No. Developing Failure for First Time During Interval		
	A.C.T.H.	Cortisone	Aspirin	A.C.T.H.	Cortisone	Aspirin
1–7	23	15	10	4	3	2
8–14	18	12	9	—	1	5
15–21	13	10	5	2	1	—
22–28	9	4	3	—	1	1
29–35	6	4	3	1	—	—
36–42	5	4	3	—	—	—
43–49	5	3	1	—	—	1
50–56	3	3	1	—	—	—
57–63	4 (1)	1	1	—	1 (died)	—
64th day	2	1	1	—	—	—
13th week	3 (2)	1	1	—	—	1

N.B.—Figures in parentheses indicate number of cases on given day in which failure had reappeared after previous disappearance.

at about the same rate, regardless of therapy. In all but one case in each treatment group failure disappeared by the 13th week. After initial disappearance it reappeared in only three cases, all in the A.C.T.H. group.

Among the cases *without* congestive failure at the start of therapy, 7 of 139 A.C.T.H., 7 of 152 cortisone, and 10 of 158 aspirin cases developed failure during the 13-weeks period (Table 27). In 21 of these (7 A.C.T.H., 6 cortisone, and 8 aspirin), failure appeared during the treatment period but disappeared in all but five cases during the observation period. One of these, a cortisone case, had a fatal outcome during the observation period, and four (two A.C.T.H., two aspirin) had persistent failure at the ninth week. In three cases (one A.C.T.H., two aspirin) failure was present at the 13th week. In one of these aspirin cases treatment had been changed to A.C.T.H. on the 28th and continued to the 70th day.

Thus among the cases with or without failure at the start of therapy there were no marked differences among the treatment groups in the behaviour of congestive failure.

Pericarditis was present at the start of therapy in 13 of 162 A.C.T.H., 16 of 167 cortisone, and 9 of 168 aspirin cases, and disappeared at approximately the same rate regardless of therapy (Table 28). In only four of these (two cortisone and two aspirin) did the symptom reappear following its disappearance.

Among the cases *without* pericarditis at the start of therapy (Table 28), there were 3 of 149 A.C.T.H., 3 of 151 cortisone, and 5 of 159 aspirin cases which developed pericarditis for

TABLE 28.—*Pericarditis: U.K. and U.S., all Cases*

Interval from Start of Therapy in Days	Cases with Pericarditis at Start of Therapy			Cases without Pericarditis at Start of Therapy		
	No. with Pericarditis Present on First Day of Interval			No. Developing Pericarditis for First Time During Interval		
	A.C.T.H.	Cortisone	Aspirin	A.C.T.H	Cortisone	Aspirin
1–7 ..	13	16	9	1	1	1
8–14 ..	8	8	7	2	—	2
15–21 ..	3	6	3	—	—	—
22–28 ..	2	5	3 (1)	—	—	—
29–35 ..	1	3	3 (1)	—	—	1
36–42 ..	1	2	1	—	1	—
43–49 ..	1	2	1	—	—	1
50–56 ..	1	—	1	—	1	—
57–63 ..	—	1 (1)	—	—	—	—
64th day .. 13th week	—	1 (1)	1 (1)	—	—	—
	—	—	—	—	—	—

N.B.—Figures in parentheses indicate number of cases on given days in which pericarditis had reappeared after previous disappearance.

the first time during the 13-weeks period. In nine of these (three A.C.T.H., two cortisone, and four aspirin) pericarditis appeared during the treatment period. In all 11 cases it was of short duration, persisting in no case until the ninth week, and never reappearing after disappearance.

Thus among cases with or without pericarditis at start of therapy it appeared and disappeared regardless of treatment.

Deaths

Among the 497 cases, 6 deaths occurred during the one year of follow-up. Their case histories were as follows:

Case 1.—A 12-year-old girl was admitted to a U.K. centre in her first attack, with fever, carditis with apical systolic murmur and gallop rhythm, erythema marginatum, and elevated sedimentation rate. She was treated with A.C.T.H. on the 24th day of her disease, with symptomatic improvement but with progressive carditis. A basal diastolic murmur, noted intermittently during the first week of treatment, later was constantly present, becoming associated with a basal systolic murmur. In the fourth week an apical mid-diastolic murmur was heard and nodules appeared, rapidly increasing in number. The acute disease was obviously not controlled by A.C.T.H. No additional symptoms appeared during the three-weeks observation period. The patient was kept in bed thereafter throughout her slow but progressive downhill course, death occurring five months after the beginning of treatment and one day following her removal from the hospital against advice.

Case 2.—A 7-year-old boy with a four-days history of precordial, pleural, and joint pains was admitted to his local hospital, where his sedimentation rate was found to be elevated and a diagnosis of rheumatic fever was made. He was treated with penicillin, sulphonamides, and 60 gr. (4 g.) of aspirin and 30 gr. (2 g.) of sodium bicarbonate a day for 12 days without improvement. During this period he is said to have developed "a murmur" of gradually increasing loudness. He became dyspnoeic and was transferred to a U.S. centre. On admission he was extremely ill, with fever, orthopnoea, dyspnoea, cyanosis, muffled heart sounds, apical systolic murmur, gallop rhythm, and tachycardia (146/min.). Bronchial breathing and rales were heard over both lung fields. A diagnosis of rheumatic pancarditis with mitral valvular disease and congestive heart failure was made and rheumatic pneumonia suspected. The patient was treated with digitalis and mercaptomerin ("thiomerin"), and admitted to the study in the cortisone group. He died 20 hours after admission, having received 300 mg. of cortisone. Necropsy revealed a large flabby heart with verrucae on the mitral valve and left auricular wall.

Case 3.—A 13-year-old girl with a previous history of rheumatic fever and rheumatic heart disease with mitral insufficiency was admitted to a U.S. centre on the fifth day of a recurrent attack, following an upper respiratory infection with sore throat of three weeks' duration. She was moderately ill with fever, polyarthritis, elevated sedimentation rate, and probable carditis. She was treated with cortisone for six weeks with a fairly satisfactory response, although the evidence of underlying rheumatic heart disease was unchanged. Two weeks following end of treatment, she suddenly, for the first time, went into congestive failure associated with raised temperature and erythrocyte sedimentation rate. Retreatment with cortisone was begun immediately, but she became rapidly worse and died one day later, on the 57th day after admission to the study. Necropsy revealed a greatly hypertrophied heart with obliteration of the pericardial cavity and chronic mitral disease without stenosis, bilateral pleural effusions, diffuse pulmonary oedema, and ascites. Microscopical examination showed evidence of diffuse active pancarditis.

Case 4.—A 9-year-old boy was admitted to a U.K. centre with a history of three weeks of polyarthritis with two weeks of rash. He was found to have fever, erythema marginatum, an enlarged heart, and a loud apical systolic murmur. He was admitted to the study and aspirin therapy begun. After slight improvement his temperature rose again, the heart shadow became enlarged, and a basal diastolic murmur was heard intermittently. At the end of nine weeks he was still considered to be seriously ill, and was transferred to another hospital, where he developed increasing congestive failure, which later stabilized and then gradually improved. Four months after start of treatment, while still hospitalized, he became febrile and a group A beta-haemolytic streptococcus was isolated from his throat. He was treated with penicillin but remained febrile for 12 days, after which his temperature returned to normal but signs of congestive failure progressively increased. He died one month after this relapse, five months after start of treatment. Necropsy revealed rheumatic endocarditis, myocarditis, cardiac dilatation, a bicuspid aortic valve (? congenital), and chronic venous congestion of lungs, liver, and spleen.

Case 5.—A 12-year-old boy was admitted to a U.K. centre in his second attack with pre-existing rheumatic heart disease with mitral stenosis. Rheumatic fever had continued without intermission for four months, manifesting itself by nodules, arthritis, erythema marginatum, precordial pain, and fever. Physical findings during that period were enlarged heart, apical systolic, mid-diastolic, pre-systolic, and basal diastolic murmurs, enlarged liver, pulmonary congestion, elevated sedimentation rate, and prolonged P-R interval. The patient was admitted in the aspirin group and received symptomatic benefit; relapse followed at the end of treatment. Four additional courses of aspirin were given, the patient responding in the same way each time. He was then placed on a cortisone schedule but showed no improvement, dying in the fifth week of this treatment, in congestive failure, eight months after admission to the study. Necropsy revealed rheumatic heart disease with enlarged heart, mitral stenosis, acute mitral and tricuspid endocarditis, Aschoff bodies and fibroid changes in the myocardium, congestive failure with pulmonary oedema, and cardiac cirrhosis of liver.

Case 6.—A 6-year-old boy was admitted to a U.K. centre, severely ill in the seventh week of his first (?) attack. He showed evidence of carditis with apical systolic and mid-diastolic murmurs and the signs of congestive failure. One subcutaneous nodule was noted on the right elbow. The temperature was normal and the erythrocyte sedimentation rate elevated. Because of intractable vomiting, the digitalis and aspirin were temporarily stopped late in the first week, with immediate improvement. At the beginning of the second week small doses of aspirin—20 gr. (1.3 g.) per day—were given for three days and then omitted because of lack of improvement from therapy. The patient gradually improved without treatment, but congestive failure persisted. During the fifth and sixth weeks, amidopyrine —7½ gr. (0.5 g.) per day—was given without effect on the patient's gradual improvement, which continued until the ninth week. Digitalis was then stopped and the patient discharged to a convalescent home.

The patient continued in moderate congestive failure, leading a bed-and-chair existence. Five months later he developed an upper respiratory infection, treated with sulphadimidine and penicillin. Tachycardia (145 per minute) and a pericardial friction rub developed. A six-weeks course of A.C.T.H. was given, with disappearance of acute symptoms, congestive failure continuing. The patient had a rapid increase in weight, marked moonface, and moderate hypertension, all of which gradually disappeared.

Ten months after admission to the study the patient developed another upper respiratory infection, treated with sulphonamide drugs and penicillin. He then went rapidly downhill and was transferred back to the centre, where he died in severe congestive failure after one week's treatment with A.C.T.H., digitalis, and diuretics.

Necropsy showed hypertrophy and rheumatic pneumonia, congestive failure with mitral stenosis, cardiac dilatation, acute and chronic lesions of mitral, aortic, and tricuspid valves, fibrinous pericarditis, and numerous Aschoff bodies.

In summary, there were no appreciable differences in the course of seriously ill cases, since the behaviour of congestive failure, pericarditis, or both, appeared to be similar in the treatment groups, and there were only six deaths (one on A.C.T.H., two on cortisone, and three on aspirin).

Re-treatments

Apart from the six patients who died, there were some in each treatment group who, during the one-year period, were re-treated for persisting or recurring manifestations. Thus,

re-treatment was given to 10 of the 161 A.C.T.H. patients surviving to one year. None of these re-treatments were given during the three-weeks observation period. One case was treated for chorea, and one had two courses of re-treatment. In all except the case with chorea, the symptoms demanding re-treatment were moderately severe.

Re-treatment was given to 8 of the 165 cortisone cases surviving the one year, one of which was re-treated during the observation period. All were moderately severe cases except one, having only erythema marginatum and fever. None was re-treated for chorea. One case required two re-treatments.

Re-treatment was given to 19 of 165 aspirin cases surviving to one year. Four were re-treated during the observation period, two receiving aspirin and the other two receiving cortisone. Thirteen of the 19 cases were moderately severe; of the remaining 6, 5 were re-treated for recurrent chorea and 1 for a mild illness consisting of elevated temperature and sedimentation rate.

When the cases given re-treatment are analysed according to duration of disease at start of therapy, it is seen that the differences among the three treatment groups are due entirely to the chronically ill cases. Thus in the 0–14-day group there were six A.C.T.H., four cortisone, and six aspirin cases to which re-treatment was administered. In the 15–42-day group the cases were two, one, and four, respectively; in the group of those ill 43 days or more they were two, three, and nine—a preponderance of aspirin cases in this chronically ill group.

Excluding the cases re-treated for chorea, the number of cases remains the same in the 0–14-day group, becomes one on each treatment in the 15–42-day group, and two A.C.T.H., three cortisone, and seven aspirin in the 43+-day group.

In summary, re-treatment was given to a greater proportion of cases in the aspirin than in the A.C.T.H. and cortisone groups; but this difference occurred only among the chronic cases, and was slightly affected by the larger number of cases initially admitted with chorea to the aspirin group.

Side-effects of Treatment

In both countries, practically all the A.C.T.H. and cortisone cases showed one, or a combination, of the following side-effects of therapy: moonface, hirsutism, acne, or striae. There were only 10.5% of the A.C.T.H. and 4.8% of the cortisone cases with none of these side-effects by the end of the ninth week (Table 29). These effects were recorded less frequently in the U.K. than in the U.S. cases, being absent in 15.0% of the U.K. and 6.1% of the U.S. A.C.T.H. cases, and in 10.0% of the U.K. and none of the U.S. cortisone cases.

TABLE 29.—*Side-effects of Therapy in A.C.T.H. and Cortisone Cases: U.K. and U.S., all Cases*

Side-effect	Percentage of Cases Showing Side-effect					
	A.C.T.H.			Cortisone		
	U.K.	U.S.	Total	U.K.	U.S.	Total
Moonface ..	77·5	90·2	84·0	80·0	96·6	88·6
Hirsutism ..	15·0	19·5	17·3	13·8	16·1	15·0
Acne	26·2	63·4	45·1	8·8	17·2	13·2
Striae	12·5	12·2	12·3	18·8	12·6	15·6
None	15·0	6·1	10·5	10·0	0·0	4·8
Total No. of cases ..	80	82	162	80	87	167

There were no appreciable differences between the A.C.T.H. and cortisone cases in frequency of moonface, hirsutism, or striae, but acne appeared much more often among the A.C.T.H. cases. With the exception of striae, each side-effect was recorded more frequently among the U.S. than among the U.K. cases. Although these side-effects appeared almost equally in the hormone groups, those severe enough, in the opinion of the investigator, to require stopping treatment occurred only among the A.C.T.H. cases (Table 1).

In addition to the side-effects of hormone treatment already noted, many others were reported, but, not being specifically requested, they were not uniformly recorded. These included cases of hypertension, mental symptoms, convulsions, renal haemorrhage, water and salt retention, glycosuria, infections, hepatomegaly, febrile reactions, pigmentation, increased fat deposition, and unusual increase in appetite.*

Relatively few aspirin cases developed side-effects, and these all appeared in the first week of therapy in both countries while the dosage was relatively high. In the U.K., among 80 cases there were four with tinnitus or deafness, seven with nausea, and one with hyperventilation. Comparable figures in the 88 U.S. cases were 9, 19, and 5. The few side-effects and the maintenance of the dosage schedule of aspirin without interruption, except in a rare case, suggests that these cases did not receive the maximum tolerated dosage.

In summary, very few patients in the hormone groups did not exhibit one or more side-effects. Further, there was little difference between U.S. and U.K. cases on differing schedules of A.C.T.H. or between those on A.C.T.H. and those on cortisone in either country (Table 29). In other words, the dosages of both hormones were large enough to produce a recognizable side-effect in nearly all cases.

Discussion and Conclusions

The object of the present co-operative study, set up in 1950, was to measure the relative effects of A.C.T.H., cortisone, and aspirin when given uniformly in all centres according to defined schedules. These schedules (dosages, periods of administration, and auxiliary therapy) were based mainly upon existent knowledge regarding apparent efficacy and toxicity. They had also to be practicable, not only in the length of time that patients could be kept in hospital during the trial itself, but to allow their subsequent application in medical practice if they proved to have value. It is obvious that innumerable other studies could be designed employing larger (or smaller) dosages, longer (or shorter) periods of treatment, or individualized dosage schedules which would need to be based on predetermined criteria for changes in dosage. It cannot be maintained that such other schedules are either more or less effective than those used here without adequate controlled study.

Evaluation of treatment of such a complex and not wholly understood disease as rheumatic fever poses a large number of problems. Acute rheumatic fever may be considered a specific type of generalized inflammatory reaction, but no means are available for measuring this quantitatively. Since it is impossible to correlate the observed manifestations with the severity of the pathological process, it must be accepted that the available data may represent only approximate indices of the severity of the disease. Furthermore, since many of the clinical evaluations are subjective, their interpretation must take into account observer error and acuity. For example, although there is general agreement on the importance of apical mid-diastolic murmurs as an index of carditis, inconsistencies in reporting them and difficulties in distinguishing them from a third heart sound or gallop rhythm gave this index uncertain value in this study. In general, such difficulties were reduced by the large number of patients in each treatment group and by the equal allocation of the three drugs within each study centre.

Other difficulties encountered in the evaluation of certain data were the lack of normal standards and the absence of normal values to serve as base lines at start of therapy. Moreover, variables which have been analysed separately may be interdependent. An example of these difficulties is interpretation of the changes in P–R intervals with changing pulse rates and heart size.

*With an initial average body weight of a little less than 70 lb. (32 kg.) in each treatment group, patients on A.C.T.H. and cortisone gained by the end of the ninth week an average of 11.3 and 11.8 lb. (5.13 and 5.35 kg.), whereas those on aspirin gained an average of 4.3 lb. (1.95 kg.).

In addition to grouping by duration of disease, various types of classification of patients were made. The most useful was based on the presence or absence of cardiac involvement on admission to the study. Owing, however, to the random allocation of patients to treatment and the consequent balance of characteristics, such additional groupings had roughly equal numbers in the three treatment groups. Each manifestation was analysed in several ways, and that method chosen for presentation which gave the clearest picture.

It should be noted that nowhere in this report have analyses of combinations of measurements and clinical signs been presented. Since in clinical practice the patient is assessed as a whole, attempts were made to integrate the separate manifestations in individual patients. These attempts were unsuccessful in providing new information, but, observing each case over the entire 6–9-weeks observation period, the proportion without any manifestation of rheumatic fever was found to be greater in the aspirin than in either of the hormone groups. This difference was observed whether or not a murmur at this time (6–9 weeks) was considered to be a manifestation. Thus, including a murmur as a manifestation, there were, with no manifestations at all, 11 cases on A.C.T.H., 11 on cortisone, and 25 on aspirin. This difference, however, is almost entirely due to the smaller proportion with an elevated erythrocyte sedimentation rate and/or raised pulse rate among the cases in the aspirin group. Adding the cases with only these signs to the group showing no manifestations, the numbers of the latter become 34 on A.C.T.H., 32 on cortisone, and 34 on aspirin. If the presence of a murmur at this time (6–9 weeks) is not regarded as a manifestation, the numbers with no manifestations during the whole 6–9-weeks period were 31 on A.C.T.H., 26 on cortisone, and 53 on aspirin. Adding to these the cases with only an elevated erythrocyte sedimentation rate and/or raised pulse rate, the figures become 71 on A.C.T.H., 62 on cortisone, and 72 on aspirin.

In attempting to assess the relative efficacy of A.C.T.H., cortisone, and aspirin in altering the acute disease or suppressing its manifestations, the following conclusions appear permissible.

1. During the acute illness and the first year of follow-up very few deaths occurred—one in the A.C.T.H., two in the cortisone, and three in the aspirin group. Re-treatments were given to some cases in all three groups, but apart from a slight excess in the late-treated cases on aspirin, there was no marked difference in the groups.

2. The temperature and pulse rate during sleep returned to normal during treatment in the great majority of cases in all treatment groups, but there was a greater tendency in the groups treated with the hormones for the rates to become elevated in the 6–9-weeks observation period.

3. The erythrocyte sedimentation rate decreased more rapidly during treatment in the hormone-treated groups, but was elevated more frequently in the 6–9-weeks observation period. There were no differences between the treatment groups at the 13th week.

4. The behaviour of joint involvement, chorea, and erythema marginatum was essentially the same in the three treatment groups. Nodules, however, disappeared more rapidly in the patients treated with A.C.T.H. and cortisone, although new nodules appeared in some patients during treatment in all three groups.

5. The analysis of the effects of the drugs on carditis, while undoubtedly most important, is especially difficult, and the conclusions the least clear. The following, however, seem justified :

(*a*) There appeared to be no relationship between the treatment given and the behaviour of congestive failure and pericarditis.

(*b*) There was more frequently an increase in heart size as measured by a change of 0.6 cm. or more in each of the hormone groups as compared with the aspirin group. This may be related to a possible increase in blood volume or, in some cases, to abdominal distension. It was not related consistently to weight gain, since heart size increased frequently in the 0–3-weeks period of treatment and much less frequently in the observation period (6–9 weeks) although the average weight gain during these two periods was very similar. At the one-year follow-up examination there was no appreciable difference between the three groups.

(*c*) The appearance for the first time of apical systolic murmurs was infrequent in all three treatment groups and unrelated to therapy. No consistent difference in the behaviour of murmurs present at the start of treatment was noted except that the soft apical systolic murmurs disappeared more rapidly in hormone-treated groups. At the end of one year, however, no significant difference remained. The differences in the treatment groups with respect to apical mid-diastolic murmurs in the U.K. and basal diastolic murmurs at one U.K. centre have been discussed.

(*d*) The P–R intervals decreased more frequently and more rapidly in the hormone groups than in the aspirin group. This difference between the groups lessened during the observation period and was absent at nine weeks and one year. Since the values at these later times might be closer to normal than those recorded during acute illness, it may be questioned whether the early decrease is an effect of the hormones on the disease or merely a direct effect on atrioventricular conduction time.

(*e*) At one year the proportion with residual cardiac damage was similar in the three treatment groups. A final determination of cardiac status must await results of a prolonged follow-up.

It is apparent that this study presents no evidence that rheumatic fever in children can be uniformly terminated by any of the three agents. There is evidence that hormone treatment results in more prompt control of certain acute manifestations, but this more rapid disappearance is balanced by a greater tendency for them to reappear for a limited period of time at the end of treatment. Treatment with the hormones also leads to the more rapid disappearance of nodules and of soft apical systolic murmurs. At the end of one year, however, it is clear that there was no significant difference between the treatment groups in the status of the heart.

Summary

Six centres in the United Kingdom, five in the United States, and one in Canada have collaborated in a trial of the relative merits of A.C.T.H., cortisone, and aspirin in the treatment of acute rheumatic fever and the prevention of rheumatic heart disease. The present report relates to children under the age of 16 and compares the effects of the three drugs on the acute course of the disease and on the persistence and development of rheumatic heart disease through one subsequent year.

The records of 497 patients are presented (240 U.K. and 257 U.S., including the Canadian centre in the latter). Each case met specified diagnostic criteria on admission to the trial and was allocated at random to treatment with one of the three drugs. Each treatment was given for six weeks according to a defined schedule, and detailed observations were continued for a further three weeks. Follow-up examinations were made at specified times after these nine weeks, and the present report extends to the examination made one year later —that is, 61 weeks from the start of treatment.

The study was designed to ensure a balance of cases in the three treatment groups for each centre, for the duration of illness at start of treatment, and for the time of year when cases were admitted. Random allocation of cases within this balanced design was relied upon to secure a reasonably equal distribution of cases according to age, sex, and severity and frequency of manifestations of disease. This design permits many comparisons of the total groups on each treatment.

In 51% of the patients, treatment was begun within 14 days of the onset of the attack ; in nearly two-thirds there was no history of a previous attack or evidence of pre-existing rheumatic heart disease. The treatments were therefore tested on patients of whom a large proportion were still in the early stages of the disease and had no established heart disease.

The three randomly constructed groups on A.C.T.H. (162 cases), cortisone (167 cases), and aspirin (168 cases) were notably alike in most respects at the start of the trial. The results of the treatments were measured in relation to separate manifestations of the disease—namely, temperature, pulse rate during sleep, erythrocyte sedimentation rate, joint involvement, chorea, erythema marginatum, nodules, and such aspects of the status of the heart as heart size, atrioventricular conduction time, murmurs, and, in particular, those indicative of serious illness, congestive failure, and pericarditis.

There was no evidence that any of the three agents resulted in uniform termination of the disease, and on all treatments some patients developed fresh manifestations during treatment. Treatment with either of the hormones resulted in more prompt control of certain acute manifestations, but this more rapid disappearance was balanced by a greater tendency for the acute manifestations to reappear for a limited period upon cessation of treatment. Treatment with the hormones also led to more rapid disappearance of nodules and soft apical systolic murmurs. At the end of one year there was no significant difference between the three treatment groups in the status of the heart. During the period of treatment, observation, and one year of follow-up there were only six deaths among the 497 cases, under the age of 16, admitted to this study.

The National Heart Institute of the United States Public Health Service supported the study with grants to the co-ordinating centre and to the co-operating centres in the United States and by a travel grant to the Medical Research Council of Great Britain. The Medical Research Council provided support for the six centres and for a co-ordinating registrar in the United Kingdom. The centre in Toronto received a grant from the Canadian Arthritis and Rheumatism Society. In the United States, the costs of the medical care of its patients were met by each co-operating centre, and in Great Britain by the National Health Service. The American Heart Association provided office space for the American Co-ordinating Centre and a grant for statistical services.

This co-operative clinical trial was first proposed by Dr. John R. Mote, then assistant general manager of the Armour Laboratories. For the planning of the study, funds were provided by Armour Laboratories and Merck and Company, and space and services by the Helen Hay Whitney Foundation.

Grateful acknowledgment is made to the resident and technical staffs at the co-operating centres, without whose devoted efforts the collection of these data would have been impossible.

In the planning and conduct of this trial much is owed to the wise advice and guidance of the late Dr. T. Duckett Jones and the late Sir James Spence.

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APPENDIX

Form 1

ADMISSION REPORT

1. Hosp. No. ..... 2. Study No. ..... (*from assignment envelope*)
3. Study centre ..... 4. Date adm. to centre ..... 5. Date study therapy began .....
6. Name of patient ..... 7. Date of birth ..... 8. Age ..... 9. Sex ..... 10. Race .....

(*Please put a X in each relevant "box".*)

	Has condition been present in this attack	Date first observed in this attack	Is condition present at start of therapy	Used as criterion for admission to study
MAJOR CRITERIA				
11. Active Carditis	Yes ☐ No ☐	.....	Yes ☐ No ☐	Yes ☐ No ☐
a. Development of or change in murmurs	Yes ☐ No ☐	.....	Yes ☐ No ☐	
b. Increase in heart size	Yes ☐ No ☐	.....	Yes ☐ No ☐	
c. Pericarditis	Yes ☐ No ☐	.....	Yes ☐ No ☐	
d. Congestive failure	Yes ☐ No ☐	.....	Yes ☐ No ☐	
(1) Dyspnoea	Yes ☐ No ☐	.....	Yes ☐ No ☐	
(2) Orthopnoea	Yes ☐ No ☐	.....	Yes ☐ No ☐	
(3) Liver enlargement	Yes ☐ No ☐	.....	Yes ☐ No ☐	
(4) Râles	Yes ☐ No ☐	.....	Yes ☐ No ☐	
(5) Jugular venous pressure	Yes ☐ No ☐	.....	Yes ☐ No ☐	
(6) Oedema	Yes ☐ No ☐	.....	Yes ☐ No ☐	
12. Polyarthritis (*two or more joints*)	Yes ☐ No ☐	.....	Yes ☐ No ☐	Yes ☐ No ☐
13. Chorea (*definite*)	Yes ☐ No ☐	.....	Yes ☐ No ☐	Yes ☐ No ☐
14. Nodules	Yes ☐ No ☐	.....	Yes ☐ No ☐	Yes ☐ No ☐
15. Erythema marginatum	Yes ☐ No ☐	.....	Yes ☐ No ☐	Yes ☐ No ☐
MINOR CRITERIA			Max. measurement in present attack	
16. Fever	Yes ☐ No ☐	.....	Yes ☐ No ☐	Yes ☐ No ☐
17. Elevated ESR (15 *mm./hr. or over, corrected Wintrobe*)	Yes ☐ No ☐	.....	Yes ☐ No ☐	Yes ☐ No ☐
18. Previous strep. infection	Yes ☐ No ☐	.....		Yes ☐ No ☐
a. Culture		.....		
b. ASO titre		.....	.....	
c. Sore throat with fever	Yes ☐ No ☐	.....		
19. Increased P-R interval (*see criteria*)	Yes ☐ No ☐	.....	Yes ☐ No ☐	Yes ☐ No ☐
20. Previous history of rheumatic fever or rheumatic heart disease:				Yes ☐ No ☐

a. Total No. of attacks *including* present attack ..... Reliability of history { Good ☐ Questionable ☐ Poor ☐

b. Date 1st attack ..... Manifestations .....
Date 2nd attack ..... Manifestations .....
Date 3rd attack ..... Manifestations .....

c. Residual heart damage from these or any unrecorded attacks:
(1) History of .....
(2) Present findings .....

21. Previous Therapy:	Date begun	Total amt. given	Date stopped
ACTH (*any attack*)	.....	.....	.....
Cortisone (*any attack*)	.....	.....	.....
Salicylates (*this attack*)	.....	.....	.....

SUMMARY

22. General description of progress, course, and severity of attack up to time of entry of trial:

.....
.....
.....
.....
.....

23. Present cardiac diagnosis:—Anat. .....
Physiol. .....

24. Date of onset (*present attack*) .....
25. Study group (*put X in box below*):

Duration from Onset	Age: Under 16 yrs.	Age: 16 yrs. and over
0–14 days		
15–42 „		
43 days and over		

26. Therapy group—ACTH ☐ Cort. ☐ Salic. ☐
Excluded from study ☐ "Out" ☐
(*If case was excluded from study, explain fully on back of form.*)

27. Investigator (*sign.*) .....
28. Date reported to centre .....

PROGRESS REPORT

Form 2

1. Hosp. No..... 2. Study No..... 3. Study centre.....
4. Date adm. to centre..... 5. Date study therapy began.....
6. Name of patient..... 7. Age..... 8. Sex..... 9. Race.....

10. a. Date (month and day)	*D*						
b. Days from onset	*D*						
c. Day of therapy	*D*						
11. Temp. (max. for day)	*D*						
12. Sleeping pulse	*D*						
13. Weight	*D*						
14. Blood pressure	*DW*						
15. Gallop rhythm *0 or +*	*DW*						
16. Arrhythmias *0 or +*	*DW*						
17. Murmurs	*DW*						
a. Apical organic systolic (*0—3*)							
b. Apical mid-diastolic (*0—3*)							
c. Basal diastolic (*0—3*)							
d. Apical presystolic (*0—3*)							
18. Precordial pain *0 or +*	*DW*						
19. Pericardial a. Rub *0 or +*	*DW*						
b. Effusion *0 or +*	*W*						
20. Failure *0—3*	*DW*						
a. Orthopnoea *0 or +*							
b. Dyspnoea *0 or +*							
c. Liver enlargement (*cm.*)							
d. Oedema *0 or +*							
e. Rales *0 or +*							
f. Jugular venous pressure (*cm.*)							
g.							
21. a. TD/ID (*mm./mm.*)	*W*						
b. Contour *0 or +*	*W*						
22. PR/Vent rate	*W*						
23.							
24.							
25. Joints *0—3*	*DW*						
26. Nodules *0 or number*	*DW*						
27. Erythema marg. *0 or +*	*DW*						
28. Chorea *0—3*	*DW*						
29.							
30.							
31. ASO titre	*M*						
32. ESR (*uncorrected*)	*W*						
33. Haematocrit	*W*						
34. Eosinophils	*Date*						
35. pH	*W*						
36. CO_2 (*meq.*)	*W*						
37. K (*meq.*)	*W*						
38. Urine sugar *0—3*	*W*						
39.							
40.							
41. **A.C.S.** *24 hr. dosage*	*D*						
No. doses/day	*D*						
42. KCl (*gm. p. d.*)	*D*						
43. Digitalis (*specify*)	*Date*						
44.							
45.							
46. Chemotherapy *Amt.*	*Date*						
47. Toxic symptoms *0 or +*	*D*						
48. Complications	*Date*						
49. General condition { improved / unchanged / worse }	*W*						

D daily; DW daily for days 1–7 and 42–56, otherwise weekly; W weekly; M monthly.

PROGRESS NOTES

Date	Notes	Observer

WEEKLY SUMMARY OF GENERAL CONDITION OF PATIENT

SIDE-EFFECTS OF THERAPY

Date special therapy began .....

Date special therapy ended .....

ACTH	
CORTISONE	
ACETYLSALICYLIC ACID	

Symptom	Date of first appearance	Date of disappearance	Describe severity
1. Moonface			
2. Abnormal fat deposition			
3. Hirsutism			
4. Acne			
5. Striae			
6. Amenorrhoea			
7. Mental changes (*specify*)			
a.			
b.			
c.			
d.			
8. Weakness			
9. Pigmentation			
10. Other (*specify*)			
a.			
b.			
c.			
d.			
11. Salicylism (*specify*)			
a.			
b.			
c.			
d.			
e.			

FOLLOW-UP REPORT

Form 1

1. Hosp. No..... 2. Study No..... 3. Study centre.....
4. Date adm. to centre..... 5. Date study therapy began.....
6. Name of patient ..... 7. Age..... 8. Sex.....
9. Race.....

10. Date (month and day)								
11. Fever a. Temperature								
b. History	0 or +							
12. Sleeping pulse (if I.P.)								
13. a. Weight								
b. Height (inches)								
14. Blood pressure								
15. Gallop rhythm	0 or +							
16. Arrhythmia	0 or +							
17. Murmurs								
a. Apical organic systolic	0—3							
b. Apical mid-diastolic	0—3							
c. Basal diastolic	0—3							
d. Apical presystolic	0—3							
e. Basal systolic	0—3							
18. Precordial pain								
a. At follow-up exam.	0 or +							
b. History	0 or +							
19. Pericardial a. Rub	0 or +							
b. Effusion	0 or +							
20. Failure	0—3							
a. Orthopnoea	0 or +							
b. Dyspnoea	0 or +							
c. Liver enlargement	(cm.)							
d. Oedema	0 or +							
e. Râles	0 or +							
f. Jugular venous pressure	(cm.)							
g.								
21. a. TD/ID	(mm./mm.)							
b. Contour	0 or +							
22. PR/Vent rate								
23.								
24.								
25. Joints	0—3							
26. Nodules	0 or number							
27. Erythema marg.	0 or +							
28. Chorea								
29.								
30.								
31. ASO titre								
32. ESR (uncorrected)								
33. Haematocrit								
34.								
35. Upper respiratory infection	0 or +							
36. Days in bed	0 or number							
37.								
38.								
39. Rheumatic activity	O C R or N							
40. Cardiac diagnosis								
a. Anatomical								
b. Physiological								
c. Functional capacity								
41.								
42.								
43. Digitalis therapy	(gr./day)							
44. Other therapy	0 or +							
45. Chemoprophylaxis	G P or O							
46. Urine sulphonamide	0 or +							
47. Toxicity	0 or +							
48. Examiner								

FOLLOW-UP NOTES

Date of Follow-up	Notes	Observer

A-V BLOCK AND CARDIAC OUTPUT

BY

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AND

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The Starling heart–lung preparation provides a means of determining the effect of varying degrees of A–V block and of auricular fibrillation on the output of blood from the brachio-cephalic artery of the dog. We therefore describe observations we have made in which we have produced A–V block by driving the auricles electrically at increasing rates, and also observations in which we have produced auricular fibrillation by infusing acetylcholine at a uniform rate into the blood entering the superior vena cava and applying electrical stimuli in conjunction. A description of the effects of infusing acetylcholine in this way has been given in another paper (Burn, Vaughan Williams, and Walker, 1955).

Methods

The methods employed were the same as those already described. When the heart–lung preparation of the dog was set up, leads to a Cossor electrocardiograph (model 1314) were attached to the right and left forelegs and the left hindleg. Electrodes which did not pierce the tissue were applied to the tip of the right auricle, and stimuli of 1 mA strength and of 0.9 msec. duration were applied at varying rates. In experiments on fibrillation acetylcholine was infused from a burette at known rates. The output was measured by deviating the blood before it entered the venous reservoir through a T-piece into a cylinder for a period of 15 sec.

Results

Output at Varying Rates of Stimulation

Stimuli were applied to the auricle at a rate about 20 per minute faster than the spontaneous rate. The application continued for about one minute, during which the output was measured and a record of the E.C.G. was taken. Higher rates of stimulation were then tried in succession, the range of stimuli being usually from 160 to 560 per min. During

application of the lower rates of stimulation the ventricular rate was the same as the auricular, until a rate was reached at which some of the auricular contractions were not followed by a ventricular contraction. This change is illustrated in Fig. 1, which shows that above the rate of 296

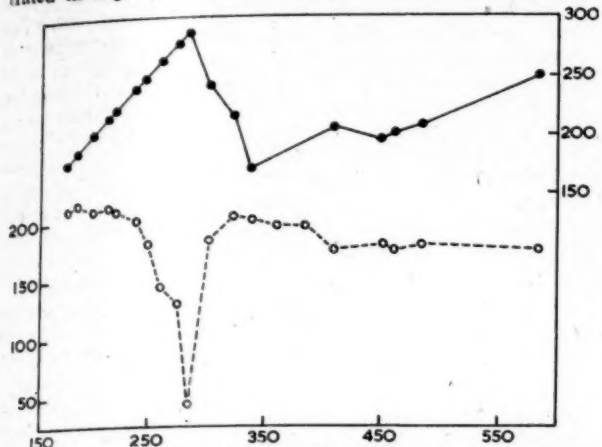

FIG. 1.—Heart-lung preparation. Abscissa: number of stimuli per minute applied to tip of right auricle. Ordinate: upper graph shows the ventricular rate; lower graph shows the output of blood in ml. per 15 seconds.

per min. further increases in the auricular rate caused a continuing fall in the ventricular rate until the latter became half the former. At this point there was a 2 : 1 block. As the auricular rate rose still further the ventricular rate followed at half the rate, and often the 2 : 1 block was unchanged up to the maximum rate of stimulation applied. In some experiments the block increased to 3 : 1 and in occasional experiments to 4 : 1; in Fig. 1 the block increased to 5 : 2 above the rate of 410 per min.

The changes in output are illustrated in Fig. 1. As the rate of stimulation increased the output remained stationary or fell slightly. With a further rise in rate the output fell steeply and continued to fall, sometimes even to zero, so long as the A/V relation was still 1 : 1. But when the rate was reached at which some auricular contractions were not followed by ventricular contractions, the output rose suddenly and returned to near its initial value. The sudden rise in output seemed to be due to the greater filling of the ventricles during the pause created by those impulses which were not transmitted to the ventricles. This explanation is supported by the relation between the ventricular rate and the output when stimulation was faster than 350 per min. (see Fig. 1). As the rate of stimulation rose to 585 per min. the ventricular rate slowly rose to 250 per min., at which point the output had gradually fallen to 175 ml. per 15 sec. But when the ventricular rate reached 250 per min. before block began, the output was also 175 ml. per 15 sec.

TABLE I.—*Restoration of Output by A–V Block. Figures are Output in ml./15 sec.*

Experiment	Before Stimulation	At Maximum Rate for V=A	When Restored by A–V Block	Degree of Block
1	164	68	150	3:2
2	170	118	152	3:2
3	154	72	136	2:1
4	168	54	174	4:3
5	154	112	150	3:2
6	170	74	146	2:1
7	170	110	146	2:1
8	180	5	178	3:2
9	168	30	178	3:2
10	182	20	172	3:2
11	174	10	166	3:2
12	186	5	180	3:2
13	196	0	172	3:2
14	212	44	204	3:2
15	194	0	141	4:3
16	170	5	160	3:2
17	182	138	176	3:2
18	176	0	146	4:3
19	200	66	170	3:2
20	190	128	168	3:2

In Table I the output changes which were observed in 20 experiments are recorded. The second column gives the output per 15 sec. before stimulation. The third column gives the output during the highest rate of stimulation at which the ventricles followed every contraction of the auricles. In all experiments the output was much reduced at this point; in Experiment 17 the reduction was only to 75% of the initial output, but in Experiments 13, 15, and 18 the reduction was to zero. The fourth column gives the output in the presence of A–V block, when it was restored to a figure similar to the initial output and occasionally greater than this. The fifth column gives the degree of block corresponding to the restored output. When the figure for the low output in the third column was expressed as a percentage of the initial output in the second column the mean value was found to be 29%. Similarly, when the figure for the restored output in the fourth column was expressed as a percentage of the initial output the mean value was found to be 92%. These results show that the spontaneous development of A–V block enabled the output to be maintained at high rates of stimulation.

Greater Output with 3 : 2 Block

When the ventricular rate fell below the auricular rate the output usually reached its greatest value when the block was 3 : 2. As the block became 2 : 1 the output fell. Figures for 11 consecutive experiments are given in Table II, which

TABLE II.—*Showing the Greater Output with* 3 : 2 *Block than with* 2 : 1 *Block*

Experiment	Block 3:2		Block 2:1	
	Ventricular Rate	Output (ml./15 sec.)	Ventricular Rate	Output (ml./15 sec.)
21	187	150	177	114
22	228	170	188	170
23	216	156	190	90
24	278	166	240	116
25	205	160	162	150
26	190	170	155	170
27	210	160	167	136
28	153	144	124	90
29	192	130	150	104
30	175	124	140	80
31	198	156	155	150

demonstrates this fall in output associated with the change from 3 : 2 to 2 : 1 block in 9 out of the 11 experiments. The ventricular rate corresponding to each output is also given. The fall in output with the fall in the ventricular rate as the block increased from 3 : 2 to 2 : 1 suggested that there was an optimal ventricular rate below which, or above which, the output fell. This optimal rate seemed to be about 200, but obviously it varied. Thus in Experiment 24 the output fell with the increase in block although the ventricular rate was still as high as 240 per min., and in Experiment 26 the output did not fall with the increase in block although the increase reduced the ventricular rate to 155 per min.

Despite the fact that the 2 : 1 block, when first reached, reduced the output, it enabled the output to be maintained when rates of stimulation were higher. For example, in Experiment 21, when the block was 3 : 2 the ventricular rate of 187 produced an output of 150 ml. per 15 sec. With a block of 2 : 1 a ventricular rate of 187 would correspond to a stimulation rate of 375 per min., at which the output should also be 150 ml. per 15 sec. Actually the output was recorded as 148 ml. per 15 sec. when the stimulation was 392 per min.

Output and Fibrillation

In some of the experiments described in the previous paper, in which acetylcholine was infused at a constant rate, with the result that when stimulation was applied auricular fibrillation occurred, we obtained evidence that fibrillation helped to maintain output, probably because of the accompanying block. An example is given in Fig. 2. In the first part of this experiment the right auricle was stimulated at increasing rates and a relation between the ventricular rate and output

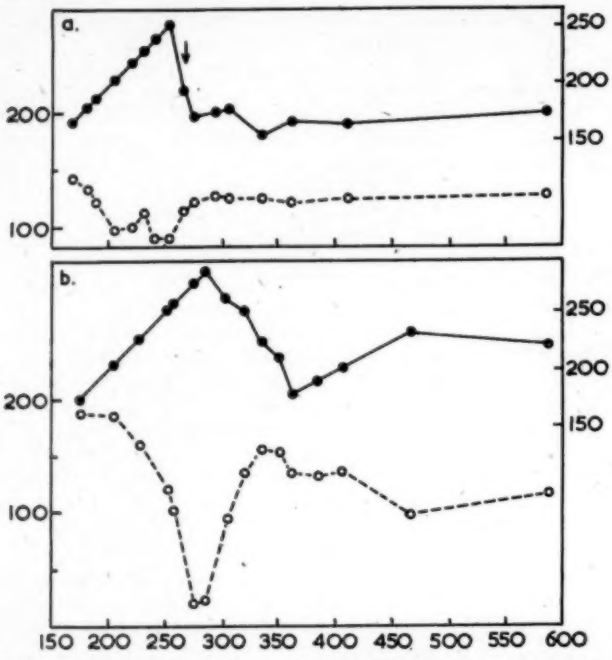

FIG. 2.—Records as in Fig. 1. (*a*) Stimulation during the infusion of acetylcholine at the rate of 200 μg./min. Auricular fibrillation began at the arrow, and the output rose in consequence. The ventricular rate and the output remained steady during stimulation up to 580 per minute. When the infusion of acetylcholine was stopped, normal rhythm returned. (*b*) Stimulation without acetylcholine infusion then led to a large fall in output, which was, however, restored when block began.

was recorded very like that seen in Fig. 1 and closely resembling that obtained later in this preparation, which is shown in Fig. 2b. In Fig. 2a acetylcholine was infused at the rate of 200 μg. per min., and when stimulation was as fast as 266 per min. the auricles began to fibrillate, and continued to fibrillate as stimulation was progressively increased to 650 per min. When stimulation was stopped the fibrillation continued, but when the acetylcholine infusion was stopped the fibrillation stopped. Before the auricle fibrillated the ventricular rate rose in step with the auricular rate up to 252 per min., and, as Fig. 2a shows, the output fell from an initial figure of 142 ml. per 15 sec. to 91 ml. With the onset of fibrillation the ventricular rate fell to 176 per min. and the output rose to 126 ml. per 15 sec. Throughout the rest of the period in which stimulation was applied at an increasing rate the ventricular rate and the output remained more or less constant. What seemed noteworthy was that when fibrillation occurred the output did not fall to zero as in the first part of the experiment. When the fibrillation stopped after discontinuing the infusion of acetylcholine the stimulation was repeated once more. The relation of ventricular rate to output is shown in Fig. 2b. It was very much the same as in the first part of the experiment, the output falling to 20 ml. per 15 sec. at a ventricular rate of 286 per min.

Discussion

The experiments which have been described have been carried out in the heart–lung preparation in which the output of blood into the systemic circulation can be measured directly. The changes in output which occurred when the tip of the right auricle was stimulated at increasing rates have been studied and the effect of A–V block in maintaining the output has been demonstrated. As the rate of stimulation rose the output fell at an increasing rate until the moment at which block began. As soon as this occurred the output promptly rose even when only 1 in 6 or more of the auricular beats was not transmitted to the ventricles. As the rate of stimulation increased, the degree of block (the proportion of non-transmitted beats) increased, and with it the output also, until the block became 3 : 2. When the block increased further to 2 : 1 the output fell slightly. Up to rates of stimulation of 500–600 per min. the output was then well maintained.

That a too-rapid ventricular rate results in a fall in output has been recognized by all workers. The occurrence of A–V block has been much studied, but for the most part it has been spoken of as though it represented an impairment of function, and almost nowhere has it been recognized as an essential mechanism for the maintenance of output when the stimuli reaching the auricles are too numerous. Block occurs spontaneously when the auricles are driven electrically in the heart–lung preparation. Once it has begun it is proportional in its degree to the rate of stimulation up to the point at which it is 2 : 1. When the block has reached this point it permits the output to be maintained even when the rate of stimulation approaches 500 per min. Thus block can be regarded as a protective mechanism to maintain the output.

There is in addition a little evidence that under certain circumstances auricular fibrillation may serve to protect the organism from the fall in cardiac output which would otherwise occur. When stimulation during the infusion of acetylcholine led to auricular fibrillation, and presumably to a high degree of A–V block, a fall in the ventricular rate occurred together with a rise in output. The ventricular rate then remained independent of the rate at which stimuli were applied to the auricle. The preservation of a reasonable output in this condition would, of course, depend on the ventricular rate being neither too fast nor too slow. It is of interest to note that three effects of acetylcholine released by vagal stimulation—namely, slowing of the pacemaker, depression of A–V conduction, and an increased tendency to auricular fibrillation—are all directed towards the same end—an optimal ventricular rate.

Summary

A study has been made of the effect of increasing rates of electrical stimulation on the ventricular rate and on the output of blood in the heart–lung preparation.

As the rate of stimulation increased, the ventricular rate also increased and the output fell. In some preparations the output fell to zero.

Block then began, some auricular beats not being transmitted to the ventricles. The output then rose promptly.

With increasing rates of stimulation the block progressively increased until it became 2 : 1, at which point it stayed, rarely becoming more than this at rates up to 550 per min. Throughout the period after the block began the output was well maintained.

Block thus acts as a mechanism whereby the ventricular rate is controlled and the cardiac output maintained; it is not necessarily a sign of impairment of cardiac function.

In experiments in which acetylcholine was infused stimulation led to auricular fibrillation. The onset of fibrillation caused a rise in output.

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Radio-isotopes are now being widely used in industry as measuring and detecting devices; for instance, a radioactive source on one outside wall of a foundry furnace and a counter on the opposite side measure accurately the height of the molten metal in the furnace. This method is also used to measure the contents of other types of containers. Again, a block in a pipe can be accurately found by moving a container holding radioactive material along one side of the pipe at the same time as a Geiger counter is moved along the opposite side.

ACQUIRED TOXOPLASMOSIS

WITH A REPORT OF A CASE OF LABORATORY INFECTION

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One of us (S. C. M.) recently became infected with *Toxoplasma gondii* when working in the laboratory. Brief mention was made of this in a recent publication on acquired toxoplasmosis (Skipper *et al.*, 1954) in which two cases of the glandular variety of the disease and one other possible case resembling typhus fever were described. The laboratory infection is now reported because it furnishes yet another example of mild adenopathy, with little constitutional disturbance, due to the toxoplasma.

Case Report

On August 31, 1953, S. C. M., for purposes of animal passage, set out to fill a sterile syringe with mouse peritoneal exudate rich in the Rh strain of toxoplasma. As the needle became blocked he removed it, set it aside point uppermost, and fitted a fresh one. Shortly afterwards he pricked his left third finger on the upturned needle. Realizing what he had done, he tried, unsuccessfully, to make the puncture bleed and applied tincture of iodine.

Nine days later (September 9) he felt shivery and tired, suffered from headache, and discovered an enlarged painful gland in the left axilla. On September 12 his temperature was 102° F. (38.9° C.) and the following day he had a rigor. In spite of a 48-hour course of penicillin, prescribed by his family doctor, his fever continued and ranged between 100 and 103.8° F. (37.8 and 39.9° C.). When examined on September 16 he was sweating and looked ill. The skin of his finger was red where it had been pricked, and two enlarged, tender, discrete glands, each the size of a walnut, were present in the left axilla. Some smaller tender glands were felt in the posterior triangles of the neck. The edge of the liver could be felt, but it was not tender. The blood count showed: Hb, 100%; red cells, 4,900,000 per c.mm.; colour index, 1; platelets, 165,000 per c.mm.; white cells, 11,000 per c.mm. (polymorphs 50%, eosinophils 2%, lymphocytes 26%, monocytes 14%, band cells 8%). Many of the lymphocytes were abnormal, resembling Downey cells types I and II. A Paul–Bunnell test was negative, as were agglutination tests for salmonella and brucella antibodies. A blood culture remained sterile.

On September 16 he was given 2 g. of sulphadimidine, followed by 1 g. six-hourly for five days, at the end of which period his temperature was normal. By September 26 the cervical adenitis had disappeared. On September 30 the total white count was 5,000 per c.mm. (polymorphs 36%, eosinophils 5%, lymphocytes 48%, monocytes 8%, band cells 2%). A few atypical lymphocytes were still present. Further Paul–Bunnell tests (on September 28 and October 23) were negative. By October 5 he felt well and had returned to work, but the enlargement of the axillary glands persisted in a minor degree until January, 1954. On May 5 full clinical examination was negative and *x*-ray films of the chest and an E.C.G. were normal. A final blood count (May 7) showed: Hb, 120%; red cells, 5,700,000; colour index, 1.05; white cells, 13,000 per c.mm. (polymorphs 78%, lymphocytes, 16%, monocytes 4%, band cells 2%). No abnormal lymphocytes were seen.

Investigations for Toxoplasmosis.—Previously, S. C. M.'s serum had repeatedly given negative results in the dye and complement-fixation tests for toxoplasmosis. Indeed, it was so free of antibody that it had been regularly used as activator in dye tests, and only four days before the accident it had been satisfactorily employed as a negative control in the rabbit skin neutralization test. Subsequent changes in titre are shown in the Table.

Changes in Titre

Date	Dye Test (Sabin and Feldman, 1948) (Beverley and Beattie, 1952)	Complement-fixation Test (Sabin, 1949)
16/9/53	1:80	Nil
27/9/53	1:200	"
9/10/53	1:600	"
21/10/53	1:1,560	1:16
27/10/53	1:3,200	1:16
16/11/53	1:4,200	1:16
8/12/53	1:2,400	1:4
8/1/54	1:1,150	1:16
5/2/54	1:1,600	1:2
12/3/54	1:2,000	1:16

On September 16 inoculation of heparinized blood into six mice, both intraperitoneally and intracerebrally, produced no illness in the animals, and two blind passages of pooled viscera, at intervals of two months, were negative. The toxoplasmin skin test (Frenkel, 1948), which was purposely postponed until February 9, 1954, was strongly positive.

Cases Already Reported

We have been able to find a total of six recorded cases of toxoplasmosis in laboratory workers (Ström, 1951; Sabin *et al.*, 1952; Sexton *et al.*, 1953; Giroud *et al.*, 1953; Franceschetti and Bamatter, 1953). It would seem that Ström's two cases were also briefly reported by Magnusson (1951).

Ström's first case was that of a woman aged 22 who, after working for only 19 days in the laboratory, developed painful adenitis of the neck with fever. She had been employed pipetting toxoplasma exudates, and it was thought infection had been by the mouth. On the third day of her illness she developed conjunctivitis, and on the fourth day a maculo-papular rash on the trunk, which disappeared in two weeks and was followed by desquamation on the hands and feet. Meanwhile the adenopathy had spread to the axillae and groins, and early in her illness the cerebrospinal fluid showed an increase in protein and in mononuclear cells (up to 12 per c.mm.) lasting for three weeks. Three weeks after the onset of the illness transient inversion of the T waves and other slighter changes in the electrocardiograph appeared and she complained of mild anginal symptoms and breathlessness. By this time her temperature was practically normal, but some weeks later severe headaches and attacks reminiscent of petit mal began, these being ascribed to meningo-encephalitis. She gradually improved but still suffered from headaches and from mild angina after six months. The duration of the lymphadenopathy was six to seven weeks. Attempts to demonstrate toxoplasms in an excised lymph node were not successful, and inoculation of mice with cerebrospinal fluid produced no illness. The dye test, at first negative, reached a titre of 1:4,000 three weeks after the onset of the illness.

Ström's second case occurred in a 22-year-old woman who pricked a finger of her left hand with a needle infected with toxoplasma material. Three days later an enlarged gland appeared in the left axilla. Her illness was very mild, and only slight enlargement of the lymph nodes in the neck, axillae, and groins was noted. A blood count was normal except for a relative lymphocytosis of 54%. The dye test was negative two weeks after infection, but gave a titre of 1:2,000 after two months.

Sexton *et al.* (1953) reported a fatal laboratory infection in a 47-year-old woman. She admitted no accident in the laboratory. After a period of four months' vague ill-health, she developed an acute febrile illness and became irrational. On the third day an extensive maculo-papular eruption, which spared the palms, soles, and scalp, appeared. There was no adenopathy. A blood count showed a leucopenia of 2,350 cells per c.mm., but later the white cells rose to 7,850 per c.mm. Moist sounds were present at the base of the right lung and there was rigidity of the limbs and to a less extent of the neck. On the seventh day of her illness convulsions began and she became deeply comatosed. The cerebrospinal fluid, previously normal, was now xanthochromic (protein 55 mg. per 100 ml., sugar 48 mg. per 100 ml., culture sterile). Treatment, which included sulphonamides, antibiotics, and, because of low plasma electrolytes, deoxycortone, was unavailing, and she died on the ninth day. The dye test, which was negative before her illness, rose to a titre of 1:256 on the eighth day and the organism was recovered from mice inoculated with whole blood and cerebrospinal fluid taken before death, and with brain, spleen, and liver emulsion obtained at necropsy. Parasites were also seen in the patient's heart muscle, which showed widespread focal myocarditis. There was extensive gelatinous oedema of the lungs with cellular proliferation in the alveoli and in the interstitial tissue.

Giroud *et al.* (1953) briefly describe, in a laboratory technician, a febrile illness accompanied by conjunctivitis, headache, and, on the sixth day, by a facial maculo-papular rash. The complement-fixation test was positive to a titre of 1:32, but a complement-fixation test for Q fever was also positive (1:40).

Sabin *et al.* (1952) mentioned that one of their number was bitten by a toxoplasma-infected rabbit. No fever or other symptoms resulted, but the dye test became positive after 16 days and reached the high titre of 1:16,000 after 30 days, while complement-fixing antibodies appeared later.

Finally, Franceschetti and Bamatter (1953) quote the case of a girl (mentioned to them by Jaeger) whose eye was splashed while manipulating a suspension of toxoplasma. She was said to have developed "relapsing meningo-encephalitis."

Discussion

Skipper *et al.* (1954) point out that acquired toxoplasmosis usually occurs in latent form, no apparent illness resulting. In describing active acquired toxoplasmosis they draw attention to its two main types. In the first, the disease runs a benign course with mild fever and adenopathy, closely simulating glandular fever. In the second, the illness is acute and sometimes fatal. In addition to adenopathy, there are protean manifestations, particularly a maculo-papular rash, pneumonia, myocardial involvement, and infection of the nervous system with the production of meningo-encephalitis. The laboratory infections here described admirably illustrate the different forms the disease may take. Skipper *et al.* (1954) draw particular attention to the glandular variety of acquired toxoplasmosis and state that the disease should be suspected in cases of lymphadenopathy of uncertain aetiology when the Paul–Bunnell test is negative. More recently, Cathie (1954a) has carried out the dye test and complement-fixation test on the sera from 20 children and young adults in whom glandular fever was suspected on clinical grounds and in whom the Paul–Bunnell test was negative. In seven cases the dye test was positive, to titres varying from 1:32 to 1:512, and in six of these the complement-fixation test was positive to a titre of from 1:16 to 1:64.

It is well known that women who bear toxoplasmic infants are latently infected and very rarely show evidence of the disease. It is therefore of interest that Farquhar and Turner (1949) published the case of a woman who during the twenty-sixth week of pregnancy suffered a short influenza-like illness accompanied by enlargement of the cervical, axillary, and inguinal glands and who subsequently bore a toxoplasmic child. In the light of recent knowledge it seems likely that the adenopathy was a clinical manifestation of active toxoplasmosis occurring during pregnancy.

The diagnostic value of the dye test and of the complement-fixation test is well shown in the case of S. C. M. Although some authorities have expressed doubt about the specificity of the dye test, so far as we are aware high titres such as we obtained in this serum have not been encountered in any other disease. Of particular importance is the rise and fall in the titre, as was emphasized by Sabin *et al.* (1952). As stated, we were unable to recover the organism from the blood by animal inoculation; we did not feel justified in excising a lymph node. Case reports show that direct demonstration of the toxoplasm in sections of affected organs and the transmission of the disease to animals by inoculation of blood, cerebrospinal fluid, or tissue emulsion is by no means always successful. Positive results are more likely to be obtained with severely ill patients. Skipper *et al.* (1954) were unsuccessful with lymph-node tissue, heparinized bone marrow, and citrated blood taken from one of their cases. Cathie (1954b), however, has reported the successful recovery of the organism by animal passage, using saliva and blood taken from a 5-year-old boy suffering from the glandular variety of the disease.

Little is yet known about the source of the infection in acquired toxoplasmosis. Although it has long been realized that the toxoplasm infests many species of animals, including domestic, direct transmission of the disease from animal to human, except, of course, in laboratory infections, has never been conclusively demonstrated. Similarly, transmission from human to human is known to occur only in the case of a woman who bears a toxoplasmic infant. Cathie (1954b) makes the interesting suggestion that one form of transmission may well be by direct contact spread through the saliva.

A large number of compounds have been tried, without success, in the treatment of experimental toxoplasmosis in animals (Eyles, 1953). So far, none of these drugs has been used in the treatment of human infections on a scale large enough to warrant drawing any conclusions. S. C. M. was treated for two days with penicillin without any effect on his pyrexia; it was not possible to ascertain whether there was a response to sulphadimidine.

Summary

A case of toxoplasmosis resulting from a finger-prick sustained in the laboratory is described. After an incubation of nine days a mild illness characterized by fever and lymphadenopathy resulted. The diagnosis was made by means of the dye test, which rose to a high titre (maximum 1:4,200), but the organism could not be recovered by animal passage.

Other published cases of laboratory toxoplasma infection collected from the literature are described. The clinical features of these cases vary, but closely resemble those of the spontaneously acquired disease. One case terminated fatally.

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ANTICHOLINESTERASES AND MUSCLE RELAXANTS

BY

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The muscle relaxants commonly used in anaesthesia achieve their action either by competing with acetylcholine at the motor end-plate—for example, gallamine and tubocurarine—or by persistently depolarizing the motor end-plate and rendering it inexcitable to acetylcholine—for example, succinylcholine and decamethonium iodide (Paton, 1953). Normal neuromuscular transmission is dependent upon the liberation of acetylcholine, which transmits the stimulus to the muscle and is thereafter immediately neutralized by the enzyme cholinesterase, which is normally present in excess. If neutralization does not take place the accumulation of acetylcholine permanently depolarizes the motor end-plate, so preventing the passage of further impulses, and produces a paralysis (Feldberg, 1951). The competitive blocking agents gallamine and tubocurarine antagonize the action of acetylcholine, whereas succinylcholine acts in the same way as an accumulation of acetylcholine, and its hydrolysis is similarly dependent upon the presence of cholinesterase, though at a slower rate (Bovet *et al.*, 1951). Decamethonium iodide, although also achieving its effect by depolarization, is not dependent upon the presence of cholinesterase for its removal (Paton and Zaimis, 1949).

The amount of cholinesterase in the body may alter the duration of action of some relaxants, and it would therefore seem that when using these drugs in cases in which the blood cholinesterase has been lowered by previous exposure to anticholinesterase substances—for example, certain insecticides—varying modifications of dosage might be needed. To determine whether in fact such modifications were necessary a comparison has been made of the periods of respiratory paralysis following intravenous injection of comparable dosages of tubocurarine, gallamine, decamethonium iodide, and succinylcholine in Rhesus monkeys before and after they received a standard dose of a known anticholinesterase. The chosen compound was sarin (*iso*-propyl-methyl-phosphono-fluoridate), which was given subcutaneously in a dose of two-thirds of the LD_{50} (the LD_{50} being the dose which is lethal to 50% of monkeys of the same species in a given series). This dosage was sufficient to cause marked symptoms of miosis, salivation, respiratory distress, and muscular fibrillation.

Technique

Rhesus monkeys of approximately 4 kg. were anaesthetized with thiopentone, 0.1 g. intravenously, and intratracheal intubation was performed with a close-fitting polythene cannula, through which the animal was ventilated at a rate of 18 a minute and a stroke volume of 50 ml. by means of a standard respiratory pump. A pneumograph was attached to the chest and a continuous record of respiratory movement obtained. The relaxant under investigation was then injected, after which 1 ml. of blood was withdrawn for plasma cholinesterase estimation. At five-minute intervals the respiration pump was disconnected for 30 seconds to ascertain whether spontaneous respiration had returned. The time of respiratory paralysis in all experiments was taken as the time from the injection of the relaxant to the re-establishment of effective natural respiration—that is, a rate and an amplitude of respiration which would lead to recovery without further application of the pump. At the end of each experiment a second 1-ml. sample of blood was withdrawn for plasma cholinesterase estimation.

The relaxants were investigated in pairs—namely, tubocurarine and decamethonium iodide, gallamine and succinylcholine—on two groups of 10 monkeys as follows :

1st week .. Gallamine 2nd „ .. Succinylcholine Monkeys then given sarin 3rd week .. Gallamine 4th „ .. Succinylcholine	}	5 monkeys
1st week .. Succinylcholine 2nd „ .. Gallamine Monkeys then given sarin 3rd week .. Succinylcholine 4th „ .. Gallamine	}	5 monkeys

Similarly, a further 10 monkeys were used for the remaining pair of relaxants.

The dosages of relaxants used were as follows : tubocurarine, 1 mg./kg. ; gallamine, 4 mg./kg. ; decamethonium iodide, 0.75 mg./kg. ; succinylcholine, 60 mg./kg. These dosages were selected, after preliminary investigations, to give 30 to 90 minutes' respiratory paralysis.

Immediately after the completion of each experiment the plasma cholinesterase estimations were carried out by Ammon's modification of Warburg's manometric method (Ammon, 1933).

Results

The results showed that there was no influence of one relaxant upon another in any experiment, and the four agents could therefore be considered independently. As

Table of Results

Monkey	Period of Respiratory Paralysis before Exposure (min.)	Days after Exposure	Period of Respiratory Paralysis after Exposure (min.)	Change (min.)
		Tubocurarine		
1	85	2	70	−15
2	115	3	75	−40
3	75	4	40	−35
4	90	4	65	−25
5	85	4	55	−30
6	75	7	100	+25
7	65	7	75	+10
8	85	8	70	−15
9	85	8	75	−10
10	75	10	70	−5
		*Decamethonium Iodide**		
11	30	3	25	−5
12	35	3	35	0
13	15	3	10	−5
14	30	4	40	+10
15	30	4	25	−5
		Gallamine		
16	95	2	80	−15
17	85	3	75	−10
18	100	4	65	−35
19	110	5	95	−15
20	95	6	75	−20
21	75	10	75	0
22	105	12	90	−15
23	110	13	90	−20
24	105	13	90	−15
25	80	14	85	+5
		Succinylcholine		
26	55	2	70	+15
27	35	3	55	+20
28	40	4	55	+15
29	35	5	55	+20
30	35	7	65	+30
31	35	7	45	+10
32	50	11	55	+5
33	35	11	35	0
34	35	12	35	0
35	30	13	30	0

* In this group, there being no significant changes in respiratory paralysis after sarin within 4 days of exposure, it was unnecessary to expose further animals.

can be seen from the Table, with tubocurarine and gallamine there was a significant decrease in the period of respiratory paralysis after sarin, whereas with succinylcholine there was a significant increase. This effect of sarin was temporary, the period of respiratory paralysis in general showing less change with a longer period of delay. Sarin had no appreciable effect on the respiratory paralysis following decamethonium iodide.

Cholinesterase Estimations.—The results obtained from the plasma cholinesterase estimations were so anomalous that no attempt was made to correlate them with the periods of respiratory paralysis. There was a wide variation between individual monkeys in their clinical response, as well as in the degree of blood cholinesterase reduction produced by sarin.

Discussion

The results of this investigation are in accordance with current theories of neuromuscular block (Paton, 1953). Tubocurarine and gallamine achieve their action by inhibiting acetylcholine at the neuromuscular junction, and this effect is antagonized by sarin. The duration of the block with succinylcholine is governed by the speed with which the drug is hydrolysed in the blood and at the end-plate; sarin, by preventing hydrolysis, prolongs the action. Since decamethonium iodide acts not by preventing the action of acetylcholine but by mimicking it, and is not destroyed by cholinesterase, anticholinesterases have no effect. The experiments showed that these changes were more marked when the relaxant was given soon after exposure to the anticholinesterase and diminished with the passage of time, presumably owing to the gradual regeneration of cholinesterase to effective physiological levels.

It is interesting to note the large dose of succinylcholine needed to produce respiratory paralysis in the monkey, approximately ten times the dose for man. There was much less species difference in the dosages of the other three drugs.

Conclusions

With the exception of decamethonium iodide, the duration of action of the relaxants commonly used in anaesthesia appears to be modified temporarily by the effects of anticholinesterase intoxication. With the extended use of these substances as insecticides the possibility of inadvertent poisoning must be considered (Barnes and Davies, 1951) if a relaxant has to be used. This may be of particular importance to Service medical officers and others who may be called upon, in the event of war, to anaesthetize casualties who have been exposed to sarin.

Summary

A description is given of a series of simple experiments designed to determine the effect of intoxication with sarin on the duration of muscular relaxation produced by tubocurarine, gallamine, succinylcholine, and decamethonium iodide.

The duration of the respiratory paralysis induced by tubocurarine and gallamine is decreased, that produced by succinylcholine is increased, and the effect of decamethonium iodide is unchanged following sarin.

The clinical implications of these results are discussed.

We are indebted to the Chief Scientist, Ministry of Supply, for permission to publish this article.

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FAMILIAL HYDRONEPHROSIS

BY

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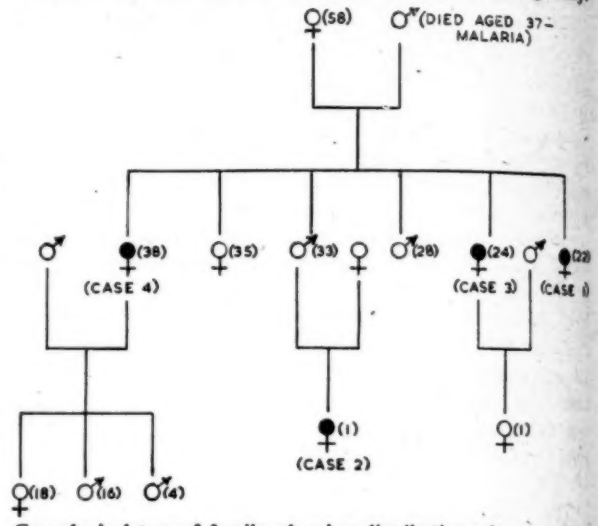
The coincidence of more than one case of hydronephrosis in a family is rare enough to attract attention. The incidence of non-calculous hydronephrosis in the family here reported is remarkable, and in view of its bearing on the aetiology of non-calculous hydronephrosis in general this occurrence is worthy of record.

Details of Family.—The constitution of the family is shown in the accompanying diagram. All the members of the family other than the four patients here described are apparently healthy and no other congenital abnormalities are known. There was no consanguinity.



Genealogical tree of family, showing distribution of cases. Ages at time of writing in parentheses.

Case 1

An unmarried girl of 19 was first seen in April, 1951. Her only complaint was of embarrassment occasioned by a generalized and gradually progressive abdominal swelling, which she had first noticed three years previously. The rate of enlargement had been noticeably greater in the preceding three months. She had no other complaints, and, in particular, there was no history of pain or disturbance of micturition. There had been no previous illnesses.

Examination revealed abdominal enlargement almost to the size of a full-term pregnancy, and on palpation this appeared to be due to a cystic swelling, localized mainly in the lower abdomen and extending up over the whole of the right side of the abdomen.

Straight *x*-ray examination showed a complete absence of gas and bowel shadows in the right half of the abdomen, and the liver, renal, and psoas outlines were not visible. All the bowel shadows were displaced to the left, apparently by a large fluid-containing cyst which was thought to be probably ovarian.

Laparotomy on May 3 revealed the tumour to be a massive right-sided hydronephrosis which contained 11 pints (6.2 litres) of fluid. Practically nothing was left of the normal renal tissue. The tumour was removed. The ureter was not dilated. No cause for the hydronephrosis was discovered. Post-operative progress was satisfactory and the patient was discharged from hospital two weeks later, since when she has remained well.

Case 2

A female infant was delivered normally at full term in February, 1953. Her birth weight was 5 lb. 2 oz. (2.3 kg.).

At birth she was noted to have a rather protuberant abdomen which contrasted markedly with the otherwise wasted appearance of the limbs, chest, and face. She was breast-fed from birth, but sucked poorly and initially vomited after her feeds, though after about three weeks this ceased. The abdominal distension increased, and appeared to be due to an ill-defined mass, dull to percussion, on the left side of the abdomen. By the end of the sixth week the infant's general condition was somewhat improved and she was feeding better, but the abdominal enlargement was still progressing. A pyelogram at this time revealed complete absence of excretion from the left kidney.

On May 1 the abdomen was explored through a left paramedian incision and the swelling was found to be due to a large left-sided hydronephrosis. The pelvis and calices were grossly dilated and the renal tissue was reduced to a mere shell. There was a well-marked uretero-pelvic junction and the ureter was not dilated. No cause for the hydronephrosis was found. Nephrectomy was performed.

The wound healed satisfactorily but the infant did not "pick up." Two weeks later she started vomiting, and gastric peristalsis was visible. This settled completely after a short course of "eumydrin," and her subsequent convalescence was uneventful, with a satisfactory weight gain. She was allowed home on June 18, since when, apart from two attacks of bronchitis, she has been well. She is, at the time of writing, a perfectly normal healthy-looking baby aged 1 year.

Case 3

This patient, a married woman of 23, was first seen in August, 1953, almost exactly a year after the delivery of a first child. She had been perfectly well during the pregnancy. Her presenting complaint was of a dull ache in the right loin which had started two weeks previously. In the preceding week she had felt generally ill, with occasional nausea and vomiting, had complained of headaches, and had sweated profusely. Micturition was frequent and somewhat painful, and she had to rise two or three times at night to pass water. There had been no previous illnesses.

Examination revealed a healthy-looking but febrile woman with herpes labialis. There was a tender cystic mass in the right flank which was thought clinically to be a hydronephrosis. The urine contained albumin and a deposit which microscopy confirmed as pus. Bacteriological examination produced a pure culture of *Bact. coli*. The infection settled quickly with alkalis and sulphonamides by mouth, and she was admitted to hospital one week later for further investigation.

At operation on September 18 the right kidney was removed through a right lumbar incision. It consisted of a thin shell of kidney tissue round a grossly distended pelvis. A large leash of blood vessels was observed at the uretero-pelvic junction. Post-operatively, recovery was uninterrupted and she has been perfectly well since.

Case 4

A married woman of 37, the mother of three children, aged 17, 15, and 3, was first seen in June, 1953. During her last pregnancy she had suffered from pre-eclampsia, but the obstetric history was otherwise normal. There had been no other illness. On June 26 she had noted a sudden onset of pain in the right loin during the afternoon. This was associated with vomiting. She felt generally unwell and had to go to bed. When first seen later that day she complained also of headache, pain on micturition, frequency, and sweats. There was marked right-sided renal tenderness but no palpable mass. The urine showed numerous pus cells in an uncentrifuged specimen. The blood pressure was 150/90. She had a course of alkalis and sulphonamides by mouth, and after a week felt perfectly well, was afebrile, and was again up and about. There was then no albumin or microscopical abnormality in the urine. She refused further investigation.

On September 11 she was again seen with a recurrence of pain in the right loin of one week's duration, less severe but more persistent than that experienced previously. There were no febrile symptoms on this occasion and no disturbance of micturition. A cystic mass, clinically a hydronephrosis, was now palpable in the right flank. The urine showed a trace of albumin, a deposit of pus, and a growth of *Bact. coli* on culture.

Intravenous pyelography two weeks later revealed a somewhat enlarged right renal outline. Both kidneys excreted the dye. There was very well marked caliceal hydronephrosis on the right, but the pelvis and ureter contained no visible dye.

On October 16 a right lumbar nephrectomy was performed. There was gross caliceal and pelvic hydronephrosis. The ureter was of normal dimensions. The post-operative course was satisfactory and she was discharged from hospital three weeks later. Since then she has remained well.

Discussion

The occurrence of four cases of non-calculous hydronephrosis in two generations of one family would appear to rule out coincidence as an explanation. All the patients were females. In one generation three out of four sisters were affected. I have not been able to examine the other, apparently healthy, members of this family to see if any present a symptomless hydronephrosis, but obviously such a possibility exists, since the cases here reported came under observation only because of the large size of the tumour or because of the accident of infection. Thus in Case 1 the hydronephrotic sac had reached enormous proportions, containing 11 pints (6.2 litres) of fluid; in Case 2 abdominal enlargement due to the hydronephrosis was already present at birth; and Cases 3 and 4 presented with the signs and symptoms of a urinary infection.

In speaking of the aetiology of hydronephrosis Winsbury-White (1951) states: "Heredity can claim some cases." A search of the literature, however, reveals few reported cases of familial hydronephrosis. Blackwood (1896) quotes Virchow as having described the case of a woman who gave birth to three premature children, each with hydronephrosis. The cases in the family reported by Mackay (1944) differ from those here described in that they were associated with megaloureter. The history in this family was remarkable. Of seven siblings, five had congenital kidney lesions, three having megaloureters (in one bilateral) and two having congenital sarcomata of the kidney. The paternal grandfather had had a calculous pyonephrosis and may therefore have had a congenital hydronephrosis. Aaron and Robbins (1948) reported the cases of two brothers, aged 12 and 16, with hydronephrosis. In both "aberrant lower pole vessels were definitely established as the cause of hydronephrosis."

The pathogenesis of the hydronephrosis in the cases reported here is obscure. In only two is there any suggestion of a definite cause—in Case 3, which presented following pregnancy and in which aberrant vessels were reported at operation, and in Case 4, in which the patient had had three pregnancies, the last three years previously. There was no history of pyelitis of pregnancy in either of these women. Unless the remarkable familial incidence is ascribed to coincidence alone, the underlying causal factor must be presumed to have been the same in each case. Neither the aberrant vessels, present in one case only, nor pregnancy, which had occurred in only two, could therefore be of primary aetiological significance. This supports the belief of Winsbury-White (1925) that the vascular factor is of merely secondary significance in the aetiology of hydronephrosis. He contends that obstruction of the ureter by a blood vessel occurs simply as an additional factor when the renal pelvis, dilating from some other cause, reaches a sufficient degree of distension, though it may add a very severe mechanical obstruction to the primary cause of the dilatation, whatever that happens to be.

If we disregard, then, the aberrant vessels reported at operation in Case 3, we are left with the problem of the cause of the hydronephrosis in all four cases. In each the

ureter was apparently normal; the pelvis and calices alone were dilated; the uretero-pelvic junction was well marked; and yet no cause of ureteric obstruction was found.

Jewett (1940), after careful study, showed that normally there is no absolute uretero-pelvic junction, the pelvis blending into the ureter in a funnel-shaped prolongation. He believed that when such a junction exists, as it did in the cases described here, stenosis should be considered, particularly if there is pyelectasis. The fact that he considered this stenosis often congenital, since there were no acquired factors to explain it, would make such a mechanism an exceedingly attractive explanation for the present series of familial cases. However, no evidence of stenosis was found. *Faute de mieux*, we must therefore fall back on such a conception as inadequacy of the ureter as an efficient urinary duct which has been posited as a causal factor in hydronephrosis; or we must postulate a functional defect in the neuromuscular mechanism of the renal pelvis, as the familial and inherited primary aetiological factor, though there is no positive evidence for either supposition. Consideration of the familial nature of these cases does, however, serve to show that, contrary to general opinion, a pelvic and caliceal hydronephrosis of this type can occur as a congenital condition without evidence of ureteric obstruction.

Summary

Four cases of non-calculous hydronephrosis occurring in two generations of a family are described. The literature is reviewed. The aetiology of the condition is discussed.

I am indebted to Mr. R. J. Rutherford, who was responsible for the surgical care of Case 1; to Mr. M. C. Pinkerton, who was similarly responsible for Cases 2, 3, and 4; and to Dr. C. H. Kitchen, who carried out the radiological examinations.

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UNUSUAL CASE OF JUVENILE G.P.I.

BY

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AND

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Juvenile general paralysis is commonly thought to manifest itself as a gradual dementing process similar to that seen in the adult disease, but with the differences in symptomatic conduct and behaviour disorder that the onset in childhood or the school years would produce. Thus intellectual deterioration may appear as a failure to ascend the normal educational ladder or as an unexpected loss of already acquired learning. Grandiose delusions, which are uncommon, may take the form of claiming ownership of vast stores of sweets or toys. Reduced social standards, such as minor dishonesty or lack of personal cleanliness and tidiness, often presenting symptoms in adults, are likely to be less readily noticed in the juvenile age group. This is the picture given in the standard textbooks of neurology and psychiatry, though Ford (1949) and others mention a maniacal reaction as an occasional presenting symptom.

The following case is worth recording because juvenile G.P.I. is now an uncommon disease and because the method of presentation was unusual. The sudden development of a hemiplegia drew attention to the disease, and shortly thereafter the patient developed an acute mania.

Case History

A National Service man, aged 19, was admitted to Wheatley Military Hospital in July, 1953. On the previous day, while picking peas on leave at home, he had suddenly "collapsed" in a semicomatose state, from which he could be roused only by repeated shouted requests. He was able to obey simple commands, but his answers to questions were incoherent and unintelligible. On examination he proved to have a right hemiparesis with dysphasia and right homonymous hemianopsia. There were some continuous clonic movements of the right face and hand resembling epilepsia partialis continua. The pupils were large, irregular, and did not react to light. The optic fundi were normal, as were other bodily systems. The blood pressure was 140/90. The urine was free from albumin and sugar. Lumbar puncture revealed a clear fluid under normal pressure, with a protein of 70 mg. per 100 ml. and 25 white cells per c.mm. (90% lymphocytes, 10% polymorphs). His electroencephalogram showed high-voltage delta activity in both hemispheres but focusing on the left mid-parietal electrode.

During the next 48 hours his comatose condition gave place to an acute mania. He would laugh and talk continually, and as he was still dysphasic a stream of jargon, often shouted at the top of his voice, resulted. Despite his hemiparesis he made continual attempts to get out of bed, and would keep on neither bedclothes nor pyjamas. He would try to attack anyone approaching him, and when restrained in bed made continual restless movements of his non-paretic limbs. He was incontinent of urine and faeces, and had to be tube-fed. In view of a possible left frontal abscess or tumour, a carotid angiogram was done, but this showed no convincing abnormality. By this time, some five days after admission, a strongly positive W.R. in the blood and C.S.F. had been returned, and the Lange gold curve was 4555555321. The diagnosis of juvenile G.P.I. was thus suggested, and he was given penicillin, and in view of a possible gummatous process this was combined with potassium iodide. During three weeks he had 22 mega units of penicillin and 30 gr. (2 g.) of potassium iodide three times a day. On the mental side the response was dramatic. Within a week his acute mania had subsided and he would remain in bed and feed himself. He was continent of faeces, though he still occasionally wet himself.

Four weeks later he was up and helping with ward duties, though still rather emotionally labile. His neurological condition had also improved. The involuntary movements lessened gradually and ceased after some seven days, the hemianopsia and hemiparesis also cleared, though pyramidal signs—increased tendon-jerks and an extensor plantar response—remained. Some dysphasia also persisted, and there was slight proprioceptive sensory loss in the right arm and leg. The pupils remained large and irregular. There were no other signs of congenital syphilis. His electroencephalogram became more normal, with an 11 c.p.s. alpha rhythm in the right hemisphere, and some low-voltage theta activity from the anterior leads on the left. He proved to be entirely right-handed. Three months after the onset of his illness he was well enough to return home and was invalided from the Army.

As his serology remained positive he was treated with two further courses of 20 mega units of penicillin at the Queen Elizabeth Hospital, Birmingham. In March, 1954, his C.S.F. showed a protein of 42 mg. per 100 ml., with 1 lymphocyte per c.mm., Lange 3211000000, and a positive W.R. He was still emotionally labile, had occasional dysphasia and also evidence of left parietal lobe dysfunction, such as visual and tactile inattention to the right half of the body and a disinclination to use these limbs. However, he was leading a normal social life at home and was hoping to restart work in his previous trade.

Subsequent inquiries revealed that the patient had been to an ordinary school, and, although considered backward, had attended a junior technical college for a year, leaving at the age of 15. He had been employed as a factory hand and later as a storeman before his national service. On entering the Army at the age of 18, he had been regarded as rather dull and mentally immature, but no physical abnormalities were found. Three months before the illness here reported he had "collapsed" during a battle course done as part of his Army training, and a weakness of the right hand had been noted in examination. This had cleared in a few days, and he had been returned to duty but excused further battle courses.

His father, mother, and only sister each proved to have a positive W.R.

Discussion

The rarity of juvenile G.P.I. was emphasized by Worster-Drought (1940). This case also showed several uncommon features. The clinical onset was abrupt, and, although some degree of dementia may have been present for a time before the acute breakdown, it was not sufficient to prevent his wage-earning employment or his acceptance for national service. The presentation with focal neurological signs is unusual. However, such a syndrome in G.P.I. was recognized by Lissauer and Storch (1901), and these cases are sometimes referred to as "Lissauer's paralysis." Lissauer himself explained them as being due to an intense localized atrophy of a group of convolutions, but of the same pathogenesis as the more diffuse cerebral atrophy of G.P.I. More recently, however, Stewart (1933), in reviewing the pathology of juvenile cases, could find little to differentiate histologically between ordinary G.P.I. and Lissauer's type, as localized atrophy with status spongiosus occurred in both. In our case the abrupt onset of hemiparesis, the focal clonic movements, the localized electroencephalographic abnormality, and the rapid improvement with potassium iodide and penicillin, with slight residual focal signs, all suggest that a meningovascular process with gumma formation may have been present in addition to the G.P.I.; and, indeed, this may be the explanation for other cases of "Lissauer's paralysis."

A predominantly manic psychiatric picture is also unusual, though recorded in this condition. This patient's initial response to penicillin was very striking. His subsequent improvement has continued, though more slowly, and it can certainly be said that already, during the course of a year since the diagnosis was made, progress has been much better than with older remedies such as malaria, arsenic, and bismuth. Worster-Drought (1951) has used a combination of penicillin and malaria in treating 10 cases of juvenile G.P.I., with improvement in all cases. However, it is still a matter of debate whether such a combination has any advantages over penicillin alone, used, as in the acquired form of G.P.I., in large and repeated doses until the serology shows a definite response. Either way, treatment should be continued until such a response does occur.

We should like to thank Professor P. C. Cloake for the follow-up notes of the case, and the Director-General, Army Medical Services, for permission to publish.

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Spastic and other disabled children in hospitals and special schools are finding the use of magnetic letters both entertaining and instructive. Clinging to the surface of special blackboards, which can be held in any position, these letters are particularly helpful in the education of children who have to lie on their backs.

ANAPHYLACTIC SHOCK AS A COMPLICATION OF INSULIN COMA THERAPY

BY

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AND

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Changes in insulin sensitivity are fairly common during insulin coma therapy and are shown by changes in the time and depth of coma, usually in the direction of increased sensitivity, requiring reduction of the original coma-producing dose. Insulin hypersensitivity (or allergy) is far less common and actual anaphylactic shock is extremely rare.

Case Report

A 40-year-old male paranoid schizophrenic was admitted to hospital on October 15, 1953. He had been in hospital in 1950 (when he had a three-weeks course of modified insulin) and in 1952. There was no personal or family history of allergy. He was in satisfactory physical health, and routine blood investigations were normal. After preliminary electroplexy, modified by relaxants, he began deep insulin therapy on October 22. This was administered by the routine technique modified by the use of intravenous insulin. Daily injections of insulin were given for six days a week, at first intramuscularly, beginning with 10 units, then 20 units, then increasing daily by 20 units, changing to intravenous injection at 60 units. Various brands of soluble insulin of 20 units per ml. strength were used in the treatment unit, but only one batch was in use at any particular time.

November 1 was a rest day, and on the 2nd an intravenous injection of 160 units of soluble insulin was given at the usual slow speed at 7.50 a.m. This was the tenth treatment, and the dose was the same as that administered on October 31, when only sweating had resulted, with termination of the hypoglycaemia by oral glucose at 10.30 a.m. No untoward reactions had previously been noted. On this occasion, however, five minutes after injection coughing and retching occurred. The manifestation of anaphylaxis was immediately suspected, and during the preparation of an adrenaline injection severe bronchospasm occurred with startling rapidity and severity, and the patient became pallid and cold. Intravenous adrenaline tartrate, 2 ml. of 1 in 1,000 solution, was given, and general treatment for shock was begun. Bronchospasm and vasomotor collapse remained very pronounced, and consecutive intravenous injections of 60 ml. of 33⅓% dextrose solution and 2 ml. of nikethamide were given, accompanied by continuous insufflation of oxygen (later changed to oxygen with 5% carbon dioxide). Slow intermittent intravenous injection of adrenaline was maintained, and between 8 and 8.35 a.m. 8 ml. of 1 in 1,000 solution was administered. The case proceeded as follows.

At 8.40 a.m. he was given atropine sulphate, 0.6 mg. (1/100 gr.), and aminophylline, 0.5 g., intramuscularly and 33⅓% dextrose, 60 ml., intravenously. He was now sufficiently recovered to ingest chlorcyclizine hydrochloride tablets ("histantin"), 100 mg., crushed in a little glucose solution. 9.5 a.m.: Blood sugar, 143 mg. per 100 ml. 9.10 a.m.: I.V. 33⅓% dextrose 60 ml., and normal saline 40 ml. 9.30 a.m.: B.P. 114/76; pulse rate, 130 a minute. 10.5 a.m.: B.P. 94/62; I.M. nikethamide 2 ml., and I.V. injection aminophylline 0.25 g.; general condition unchanged. 11 a.m.: B.P. 80/50; pulse rate, 80 a minute; blood sugar, 43 mg. per 100 ml. 11.15 a.m.: Patient suddenly became very collapsed, with dyspnoea and very weak pulse volume; I.V.

nikethamide 2 ml., I.V. 33⅓% dextrose 60 ml., and I.M. aminophylline 0.5 g. administered, with rapid improvement. 11.30 a.m.: B.P. 84/60; pulse rate, 90 a minute. 12 noon: Renewed collapse, with dyspnoea, weak pulse, and cold extremities; I.V. adrenaline 2 ml., I.M. methylamphetamine hydrochloride 10 mg., and I.V. 33⅓% dextrose 110 ml. were injected, with consequent improvement. 2 p.m.: B.P. 114/76; blood sugar, 212 mg. per 100 ml.; I.V. 33⅓% dextrose 60 ml., and I.M. methylamphetamine hydrochloride 10 mg. At 2.10 p.m. the urine contained 2% sugar. The patient was now taking frequent sips of fluids and was maintaining his general condition. 4 p.m.: Blood sugar, 132 mg. per 100 ml.; B.P. 88/58, but general condition fairly good. Conversation was rambling at times, probably due to methylamphetamine abreaction.

The systolic blood pressure remained consistently below 100 mm. despite the general improvement. Another intramuscular injection of methylamphetamine produced further abreaction, and this drug was then discontinued to avert possible exhaustion. Intramuscular nikethamide, 2 ml., was continued two-hourly throughout the night and then four-hourly; chlorcyclizine hydrochloride tablets, 100 mg., were also given four-hourly from the next morning (November 3), when the patient's improvement was well maintained, although his conversation was noted to be rambling.

On November 4 he was still rambling and confused, although accessible mentally. Nikethamide and chlorcyclizine were discontinued, and paraldehyde, 2 fl. dr. (7 ml.), was prescribed as a nocturnal sedative. Next day he was more rational and quite normal physically. Clinical psychological examination on November 14 showed no significant mental change resulting from the anaphylaxis.

Follow-up Allergy Studies

An intradermal technique was adopted, using 0.01 ml. of test solution injected from a tuberculin syringe with a fine needle. The batch of insulin in use at the time of the anaphylactic incident ("AB" insulin, 20 units per ml.) gave a strong positive reaction. Similarly strong positive skin reactions were given by all other types of insulin tested, both unmodified (Novo insulin 20-unit solution, and Boots insulin 20-unit solution) and modified (Wellcome P.Z.I. 40-unit solution, Boots I.Z.S. 40-unit solution, and Boots I.Z.S. (amorphous) 40-unit solution). Control solutions used were normal saline and 0.3% cresol (since this latter was the preservative added to the original insulin solution): these gave consistently negative results, as also did Bencard intradermal solutions of pig, beef, and mutton proteins.

At the beginning of December passive transfer of sensitivity was attempted, using four healthy non-allergic subjects: three gave positive reactions and one gave a slight positive reaction. Sensitized skin areas were prepared by the injection of 0.1 ml. of the patient's serum.

In January, 1954, when his intradermal response to soluble insulin was still strongly positive, experiments with antihistamines were carried out, and it was found that oral dosage (chlorcyclizine hydrochloride tablets, 100 mg., an hour before the injection) diminished the reaction considerably; but this remained positive, whereas coincident injection with the insulin solution, using 0.01 ml. of a 2.5% solution of mepyramine maleate (0.25 mg. of salt) with 0.01 ml. of soluble insulin (0.2 unit) achieved almost complete neutralization.

In April, intradermal testing revealed the continued presence of a strongly positive allergic reaction to insulin. It is proposed to keep this patient under observation, so that the expected waning of his allergic state may be detected by repeated tests for skin allergy and circulating skin-sensitizing antibodies (reagins).

Discussion

The occurrence of a true anaphylactic reaction was confirmed by the presence of an incubation period, the positive intradermal tests, and the detection of circulating antibodies. These features are absent in the so-called anaphylactoid response to intravenous injections (Sollmann, 1942).

Earlier literature on the allergenic properties of insulin has been well summarized by Harten and Walzer (1940) and by Yasuna (1941). The above case is an unusually severe example of the generalized reaction regarded as occurring in about 1 in 1,000 insulin users, although Ulrich *et al.* (1939) suggested that insulin allergy was relatively more frequent in the non-diabetic patient. Harten and Walzer criticized the paucity of skin-test recording in these cases and pointed out that even less often was the possible presence of circulating reagins investigated, although neither of these reactions necessarily parallels the presence or severity of clinical symptoms.

Of particular interest in the described case was the presence of the "latent period" prior to the anaphylactic incident that occurred 11 days after the first injection of the insulin course—which was itself begun two and half years after a previous course. The increased frequency of allergy (particularly generalized) when insulin therapy had been interrupted and the resemblance of the "latent period" to the incubation period of serum sickness were emphasized in the reviews by Tuft (1928), Harten and Walzer, and others. A further feature was the occurrence of the episode immediately following an insulin-free "rest day"; this can be compared with the cases of Hinko *et al.* (1941) and of Sherman *et al.* (1941). Non-diabetics are far more likely to suffer interruptions of insulin administration, and this may account for their reported greater liability to allergic reactions.

Allergy studies in the above case confirmed the activity of a specific antigen. Despite the improved purification of insulin, some authorities maintain that its apparent allergenic properties are due to minute amounts of contaminating protein material, or even to an alteration of insulin in the isolation process, rendering it a "foreign protein" (Waters and Best, 1941).

Jorpes (1949) claimed that repeated recrystallization of insulin reduced the incidence of allergenic reactions, and suggested that these were usually, if not always, due to impurities.

The antihistamine experiments demonstrated the efficacy of these drugs in neutralizing insulin allergic effects: this has been confirmed by therapeutic experience, sometimes combined with desensitization, spontaneous or induced (Hunter and Hill, 1947; Leavitt and Gastineau, 1947; Armstrong and Lloyd, 1954). In the treatment of the above case an oral antihistamine was used, but it may be that early administration of an injectable compound, unfortunately not available at the time, might have shortened the emergency period.

We wish to thank Dr. J. S. McGregor, medical superintendent, Saxondale Hospital, for permission to publish this paper; Mr. D. C. Hubbard, F.I.M.L.T., for technical assistance; and the nursing staff for their invaluable co-operation.

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ESTIMATION OF ISONICOTINIC ACID HYDRAZIDE IN BLOOD SERUM AND CEREBROSPINAL FLUID

BY

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Cuthbertson and his colleagues (1954) described a method of estimating *iso*nicotinic acid hydrazide (I.N.H., isoniazid) in blood plasma and urine that marked a considerable advance on previous methods. Their method, however, requires about 10 ml. of blood and is rather elaborate for routine purposes. Our interest in the subject has been confined to blood and cerebrospinal fluid (C.S.F.), for which it has been possible to shorten the procedure in a manner that may be of interest to others.

Method for Serum and C.S.F.

Reagents.—Acetic acid, 0.05N. Phosphate buffer *p*H 6.5: 3 vol. M/5 Na_2HPO_4 and 7 vol. M/5 KH_2PO_4. Picryl chloride solution: 35 mg. (B.D.H.) in 10 ml. ethanol. Acetic acid, 5N. *n*-Butanol.

Protein Precipitation (in test-tube, 16 by 125 mm.).

Serum.—To 1.25 ml. of serum add 7.5 ml. of water and 1.25 ml. of 0.05N acetic acid.

C.S.F.—To 1.25 ml. of C.S.F. add 7.75 ml. of water and 1 ml. of 0.05N acetic acid. (When other amounts of serum or C.S.F. are used the above proportions of 0.05N acetic acid are strictly adhered to, and the volume is always made to 10 ml.) The tubes are immersed in a bath of boiling water for about three minutes to coagulate the protein. They are then centrifuged.

Colour Reaction.—To a test-tube (16 by 125 mm.) add 8 ml. of the supernatant fluid (≡1 ml. of serum or C.S.F.), 2 ml. of buffer, and 0.25 ml. of picryl chloride solution. Heat the tube in a bath of boiling water for 20 minutes. Cool. Add 0.4 ml. of 5N acetic acid and 3 ml. of *n*-butanol, and shake vigorously for one minute. Spin, and remove the clear butanol layer into small tubes containing 2 drops of ethanol to prevent clouding. Transfer to a glass cuvette with 1-cm. light path and note the optical density at wavelength 500 mμ.

Calibration Curve.—This was constructed from a series of readings made from solutions containing 8 ml. of water, 2 ml. of buffer, and 0.25 ml. of picryl chloride solution, and containing 0, 0.5, 1, 2.5, 5, and 10 μg. of I.N.H. Such solutions were heated as described above and the optical density of the butanol extracts was measured. When no I.N.H. was present there was a reading of about 0.01 optical density. When this was subtracted from all readings a strictly linear curve in the above range was found such that the observed optical density × 34.5=μg. I.N.H.

It may be noted here that the optical density from controls containing no I.N.H. increases rapidly with light of wavelength less than about 480 mμ, whilst at greater wavelengths the optical density from the reaction product of I.N.H. and picryl chloride decreases rapidly. At 500 mμ the blank value is almost negligible and the sacrifice in sensitivity is not more than about 20%.

Serum and C.S.F.—Controls.—Under the above conditions it has been found that sera from patients who have not received I.N.H. commonly give values, expressed as I.N.H., of 1 to 2 μg. per ml., and corresponding C.S.F.s about half such values. Such blank values are somewhat reduced but not eliminated by the extraction procedure of Cuthbertson *et al.*, so that control observations are always necessary for accurate estimation. However, as the amount of serum or C.S.F. required is now moderate, proper control determinations are practicable with sample volumes ordinarily obtainable in hospital wards.

Recovery of I.N.H. Added to Serum.—The amount of I.N.H. recoverable from serum by the present method of analysis may be seen from the observations shown in the Table. With C.S.F., recovery values are rather better.

Recovery of I.N.H. Added to Serum

I.N.H. added, μg./ml. serum	0	0·4	0·8	1·2	1·6	2·0
I.N.H. recovered, % ..	Range of blanks: 1·41–2·07 μg. as I.N.H./ml.	89	87	85	82	84
Range of recovery values, %		86–95	83–95	78–92	69–88	77–90

To seven sera, in six lots each, I.N.H. was added in the amounts noted. In each case 1.25 ml. of the serum was deproteinized as described and the equivalent of 1 ml. filtrate was treated as further described for the colour reaction. The range of blank values is inserted to indicate the necessity for control determinations.

Tungstic acid may be used, as described by Cuthbertson *et al.*, for deproteinization, but the above method gives more consistent results, is simpler, and indeed yields better filtrates with C.S.F.

Summary

A simplified method suitable for routine estimation of *iso*nicotinic acid hydrazide in blood serum and cerebrospinal fluid is described.

I should like to express my appreciation to Dr. S. W. A. Kuper (Brompton Hospital, London) for details of the method of Cuthbertson *et al.* before publication; to Dr. F. D. Stott for designing the photoelectric colorimeter; and to Mr. G. J. Bowser for technical assistance.

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Medical Memoranda

Delay in Passage of a Ryle Tube Ingested Accidentally

Many papers in the medical literature have dealt with ingested foreign bodies and complications therefrom, but, so far as can be determined, none has mentioned a Ryle stomach tube as the foreign body. Furthermore, none has described arrest occurring at the duodeno-jejunal flexure. For these two reasons the following case is worth recording.

CASE REPORT

On February 16, 1953, a youth aged 16 suffering from a left pleural effusion had a Ryle tube passed to obtain a specimen of his gastric washings for examination for tubercle bacilli. During the procedure he swallowed the tube accidentally. A strong saline emetic given immediately failed to return the tube by mouth, but it was thought that it would pass through the alimentary canal without incident.

The following day a radiograph of the abdomen showed the tube high in the abdominal cavity, probably in the stomach. Seven days later, as the tube had not passed, a second radiograph was taken and this showed that its position had not materially altered. In an attempt to locate it a barium meal was given nine days after the tube had been swallowed, and the radiograph revealed part of it emerging from the barium-filled pylorus and occupying the curve of the duodenum. Following this, regular screening demonstrated the metal weight in the end of the tube to maintain a fairly constant position on the left of the vertebral column, at the level of the third lumbar transverse process, corresponding to the position of the duodeno-jejunal flexure.

Sixteen days after the ingestion of the tube a second barium meal was given, and a lateral radiograph showed the metal weight still lying posteriorly to the stomach, at the

level of the third lumbar vertebra. On the thirty-sixth day a third barium examination revealed the metal marker in roughly the same position, and it was thought highly probable that arrest had occurred at the duodeno-jejunal junction.

On the forty-third day it was decided that, as no progress had been made, the boy should have an exploratory laparotomy with a view to removal of the tube. Shortly before the date arranged for operation, on the fifty-third day, the boy was screened again, and this time the metal weight was clearly seen lying in the pelvis. Digital examination of the rectum confirmed the presence of the tube, which was hooked by the finger and withdrawn.

COMMENT

The interesting point in this case is the unusually long time (53 days) the tube remained in the alimentary canal; yet, despite this, the patient suffered no ill effects of any kind.

It seems probable from the radiological findings that the point of arrest was the duodeno-jejunal flexure, which must surely be unusual. Furthermore, after a delay there, known to have lasted 34 days and which was probably longer, the tube became dislodged and passed without further trouble.

It is reasonable to conclude, therefore, in dealing with cases of this kind, that, provided there are no symptoms, a delay of six to eight weeks is warranted before surgical removal is considered, and that, in addition, a failure of the tube to advance in the alimentary canal for as long as three to four weeks does not preclude the possibility of a natural passage.

I thank Dr. A. J. Moon for permission to publish this case.

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Occupational Calcium Necrosis of the Skin

Necrosis of the skin due to calcium chloride solution appears to be a rarity in that only two cases have so far been published. Oppenheim (1935) described its occurrence in an ice-cream maker who accidentally allowed the concentrated solution of calcium chloride used as a freezing bath to come into contact with his skin. Heppleston (1946) described it in an operator using a 40% solution of calcium chloride as a dust-laying spray in a South Wales coal-mine. The following case, in a maker of anti-freeze solution, serves to confirm the existence of calcium chloride necrosis and to stress the need for protecting the skin from this substance.

CASE REPORT

A 29-year-old Turkish labourer was employed in making a 40% solution of calcium chloride. This was marketed as an anti-freeze agent to add to water used for mixing mortar and concrete in cold weather. The manufacturing arrangements were primitive, and one day he splashed his trousers with the solution, but did not change them or wash his legs. That night he noticed considerable pain in the parts of his legs where the tops of his gum-boots had rubbed.

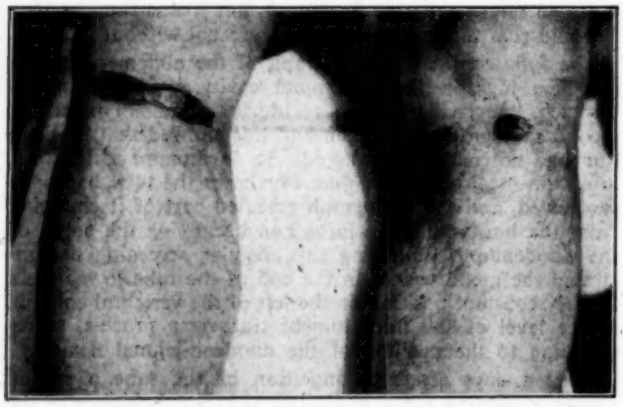

FIG. 1.—Necrosis of friction areas on the legs due to calcium chloride solution.

The next morning he reported to the industrial clinic and his legs appeared as in Fig. 1. On each was a thick black eschar surrounded by a thin border of inflammation. The appearance was similar to that of the coagulum produced by the old tannic acid treatment of burns. The eschar was obviously necrotic skin involving the full skin thickness.

With conservative treatment the coagulum began to separate along the edges on the 19th day, and was half separated on the 30th day. Healing was not complete until the 90th day.

A biopsy (Fig. 2) showed coagulative necrosis of the epidermis and underlying dermis. The latter was crowded with nuclear fragments and there was slight proliferation of fixed tissue cells in the surviving connective tissue. Von Kossa's reaction showed obvious impregnation with calcium.

FIG. 2.—Lesion of right leg, showing necrosis and calcium impregnation. Haematoxylin and eosin, Von Kossa.

COMMENT

The microscopical appearances in Heppleston's case were similar, except that in the less severe lesions there was necrosis and calcium impregnation of the dermis only. As in this case, severe lesions were present on those parts of the legs where friction from the tops of the gum-boots had occurred. Healing was prolonged, and it is for this reason that it is so important to protect the skin from calcium chloride solutions.

The cause of the lesions is probably the alkalinity of the solution combined with its necrosing effect. In the present case the *p*H of the solution was 9.4, and it was found by titration to have an alkalinity equivalent to N/50 NaOH. Calcium is a well-known necrosing agent, as shown by the dire results of its accidental injection subcutaneously or intramuscularly. The alkalinity would soften the horny layer of the skin so that penetration and subsequent necrosis could occur.

I would like to thank Dr. L. E. Glynn for kindly preparing and reporting on the section in this case.

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Reviews

KWASHIORKOR

Kwashiorkor. By H. C. Trowell, O.B.E., M.D., F.R.C.P., J. N. P. Davies, M.D., and R. F. A. Dean, Ph.D., M.R.C.P. (Pp. 308+xii; illustrated. 50s.) London: Edward Arnold (Publishers) Ltd. 1954.

A great deal of research has been done on kwashiorkor since the appearance in 1931 of Cicely Williams's classic description of the disease. Introduction of the liver biopsy technique and of new biochemical methods has given impetus to this work, and Dr. Trowell and his co-authors are able to quote over 600 references to it. When a disease of hitherto unknown causation becomes the object of much interest it is to be expected that many differing opinions will emerge, and in this respect kwashiorkor has proved no exception. There is, therefore, a need for a book, not only to draw together the widely dispersed literature on the disease, but also to mediate between varying opinions concerning it. Dr. Trowell and his associates at Mulago have been in the forefront of those carrying out research on kwashiorkor; none are more qualified to write on the subject, and they have well accomplished the task of preparing this book. It is readable, and the narrative proceeds easily from the history of the disease to the clinical features, diagnosis, pathological anatomy, biochemical findings, treatment, and prevention. There follows a discussion on protein malnutrition in adults and on the pathological and physiological implications of it and of kwashiorkor in children. There are many good photographs and diagrams.

Throughout the work the authors have put forward their own findings and views with modesty, and, though seldom leaving the reader in doubt as to their opinions, they have been careful to quote opposed views. Few will, however, disagree with their conclusion that the main features of the disease are caused by defects of protein metabolism. The use of the term "kwashiorkor" may be criticized, but this has been used advisedly. In different parts of the world innumerable terms are used for the same disease, some, such as "infantile pellagra," being sources of considerable confusion. There is need for a single generally understood term, and at present this should not imply too precise a knowledge of aetiology. There is much to be said for the term "kwashiorkor" by which the disease is known to the Ga tribe of the Gold Coast, among whom Dr. Cicely Williams carried out her original researches.

The medical world is indebted to Dr. Trowell and his associates for much of what is known about kwashiorkor. The debt is now greatly increased, for in writing this book they have performed yet another valuable service.

A. W. WOODRUFF.

RADIOISOTOPES IN MEDICINE

Radioisotope Conference, 1954. Proceedings of the Second Conference, Oxford, 19–23 July. Volume I. Medical and Physiological Applications. Edited by J. E. Johnston, assisted by R. A. Faires and R. J. Millett. (Pp. 418+xi; illustrated. 65s.) London: Butterworth's Scientific Publications. 1954.

Two important conferences have been held at Oxford on the uses of radioactive isotopes, each having been organized by the Atomic Energy Research Establishment, Harwell. The first took place in 1951, and its report, published in 1953, included about 70 papers on medical and biological radioisotope techniques (*Journal*, October 3, 1953, p. 766). The second conference met in July, 1954, and the present report is perhaps of even more value, both to those working with these methods and to anyone wishing to assess their scope or progress. Fewer communications were presented than in 1951, but they are in many cases fuller and more developed than those made at the earlier conference, though they still have the refreshing character of describing work actively in progress.

This volume gives all of the 46 medical and physiological papers presented in 1954, and the discussion following each. Fully half of these papers concern human investigation or therapy with some fifteen different radioactive elements, and the report as a whole forms a most useful source of information as to progress in new methods of investigation.

The value of this book is considerably increased by the impressively short time that elapsed between the conference in July and publication of its proceedings in November, and both the publishers and those who undertook this work at Harwell are to be congratulated and thanked for this addition to the outstanding success of the conference itself.

E. ERIC POCHIN.

CHEMISTRY OF METABOLISM

Chemical Pathways of Metabolism. Edited by David M. Greenberg. Volume II. (Pp. 383+viii. $9.50.) New York: Academic Press Inc. 1954.

This is the second volume of the work, the first volume of which was reviewed in these columns on October 30 of last year (p. 1035). The survey of existing knowledge of the metabolism of major constituents in living organisms continues with "Nitrogen Metabolism of Amino Acids" (P. P. Cohen); "Carbon Metabolism of Amino Acids" (D. M. Greenberg); "Synthetic Processes Involving Amino Acids" (D. M. Greenberg); "Metabolism of Sulphur-containing Compounds" (D. M. Greenberg); "Enzymatic Syntheses of Peptide Bonds" (H. Borsook, with an Addendum by D. M. Greenberg); "Purines and Pyrimidines" (M. P. Schulman); "Nucleotides and Nucleosides" (L. A. Heppel); and "Metabolism of Haem and Chlorophyll" (S. Granick). Thus the review proposed is completed in this volume.

The mechanism whereby protein is synthesized in living systems remains mysterious, and perusal of the relevant chapters in the volume under review leads one to no definite conclusion. The interpretation of results in which isotopically labelled amino-acids are incorporated into tissue substance is often uncertain, and the caution advisable in the assessment of the significance of results of this sort is critically discussed. One can say that the elucidation of the mechanism of protein synthesis is the most important outstanding problem in the field of intermediary metabolism; it is one that must have relevance to the nature and control of both normal and neoplastic growth.

Some overlap was unavoidable among the chapters of the present volume, but this is not such as to inflate the book unduly. The two volumes together provide an authoritative and lucid account of the present knowledge of intermediary metabolism and can be confidently recommended to those who wish to bring their knowledge of a complex field reasonably up to date.

F. G. YOUNG.

ACTINOMYCETES AND THEIR ANTIBIOTICS

Guide to the Classification and Identification of the Actinomycetes and their Antibiotics. By Selman A. Waksman and Hubert A. Lechevalier. (Pp. 246+x. 38s. 6d.) London: Baillière, Tindall and Cox. 1953.

In this useful reference volume the discoverer of streptomycin and one of his colleagues first classify the Actinomycetes and describe each species. The genus occupying most space is naturally *Streptomyces*, since it is from within this that most antibiotics since penicillin have come; 147 species are described, many of them first studied by the author himself long before the antibiotic era, and others discovered recently as antibiotic producers in the course of large-scale soil surveys. The descriptions are intended to enable workers to decide whether any newly isolated species is in fact new, and they will be helpful for this purpose, though not always conclusive.

The second part of the book is about the antibiotics formed by this class of micro-organism, which the authors divide into twelve groups. Four of these are of clinical interest on account of their antibacterial activity, and

others because of their activity against fungi, protozoa, and viruses; the remainder are of academic rather than clinical significance. It is stated that substances with anti-neoplastic properties may come to assume greater importance. There follow a key to the identification of these antibiotics and a description of each in alphabetical order, stating its source, method of extraction, chemical and physical properties, biological activity, toxicity, and uses if any. Mycologists and anyone engaged in the present search for antibiotic-forming organisms will find this book a valuable source of information.

L. P. GARROD.

CHROMATOGRAPHY

Chromatography. British Medical Bulletin, Volume 10, No. 3. (Pp. 161–252; illustrated. 15s.) London: British Council. 1954.

The distinguished contributors who have written the separate chapters to this volume make an almost unique contribution to the literature on chromatography. The introduction by Dr. A. J. P. Martin is followed by a valuable account of the general principles by Dr. R. J. P. Williams. The gas–liquid chromatography is dealt with by Drs. James and Martin, and the application to paper is covered by Dr. Consden. The remaining chapters deal with applications of the method to special problems. Those of most interest to medical readers deal with amino-acids (A. C. Chibnall), peptides (P. N. Campbell and T. S. Work), porphyrins (J. E. Falk), thyroid hormones (J. Gross), antibiotics and vitamins (T. S. G. Jones), steroids and sterols (I. E. Bush), proteins (R. R. Porter), separation of amino-acids and peptides (S. M. Partridge), and amino-acid metabolism (C. E. Dent and J. M. Walshe).

The general standard is so high that it is somewhat invidious to select any particular article. The references are well chosen and in many cases cover the literature up to the year of publication. Although most articles are confined to technical methods, some interesting new data on amino-acid metabolism are included in the last article in the book. Altogether this most useful volume has appeared at a particularly appropriate time, and all those working in the field will be grateful to the writers for their informative summaries of work on their special subjects.

N. F. MACLAGAN.

MEDICAL LIBRARIANSHIP

Proceedings of the First International Congress on Medical Librarianship. Edited by F. N. L. Poynter. *Libri*, Volume 3, 1954. (Pp. 451; illustrated. Danish kroner 50.) Copenhagen: Ejnar Munksgaard. 1954.

The professional librarian is of comparatively recent origin. "At the first national meeting of librarians in America in 1853 some 70 of the 82 gentlemen present were university professors or clergymen; while three or four were lawyers and an equal number physicians." The full-time professional medical librarian is of still more recent origin, yet their number has increased rapidly. The medical group of librarians was the first to hold an international congress, which took place in London in July, 1953. This volume contains the 61 addresses delivered at the congress and the discussions which took place upon them, well edited by Mr. F. N. L. Poynter.

Among the papers are several dealing with the function and education of the medical librarian and with systems of classification and centralization; there are also an account of medical libraries all over the world and some historical papers. Here we have a mine of information which will be constantly referred to by all interested in medical books. In the account of London medical libraries we missed any reference to that of the Medical Society of London. Among such an array of papers it is difficult to mention many, but we particularly liked the short account given by Lieutenant-Colonel Frank B. Rogers of the growth of the wonderful Armed Forces Library at Washington; the erudite article by Mr. K. W. Humphreys on the medical books of the mediaeval friars; the description of the Trew Library at Erlangen; and Dr. Bett's witty comments on the writing of papers by medical men. We quote from the last-mentioned: "Do remember that it is possible for a medical man to be a pillar of his profession and at the same time be utterly ignorant of the meaning of so hackneyed a term as *ibidem*."

Mr. W. B. McDaniel pays a nice compliment to doctors and to medical librarians when, in commenting on the statement made by two medical historians that medical librarians as a class were very helpful and companionable, he adds: "I confess that I have often felt we *were* peculiarly delightful people, for librarians. If it be true that we are, the explanation is a simple one. We serve the sons and daughters of Aesculapius—a most delightful and inspiring lot." We leave it at that.

ZACHARY COPE.

MEDICAL SHORT STORIES

Medicine in its Human Setting: Being Clinical Stories for Students, Nurses, and Practitioners. By A. E. Clark-Kennedy, M.D., F.R.C.P. Illustrations by Sylvia Treadgold, M.S.I.A. (Pp. 276; illustrated. 13s. 6d.) London: Faber and Faber, Ltd. 1954.

When Dr. Conan Doyle published *Round the Red Lamp*, a collection of medical short stories, in 1894, he was criticized for describing features of medical life which were better relegated to the lecture-room, the ward round, or the text-book. The subject was painful; then why treat it at all? To this he replied that it was the province of the novelist to describe painful things as well as cheerful ones. The course of time has changed all that, and to-day a book of medical short stories needs no apology. Authors like Treves, Francis Brett Young, A. J. Cronin, and Somerset Maugham have made use of their medical knowledge in fiction, and non-medical writers have done the same. Who can forget the masterly picture of locomotor ataxia in Kipling's story "Love o' Women," or the harrowing account of cancer in Arnold Bennett's *Riceyman Steps*?

In this book Dr. Clark-Kennedy, whose writings on the history and philosophy of medicine stimulate thought and practice, has written 22 short stories on various aspects of disease. His aims are to lighten the heavy burden of medical reading; to correct the bad habit of thinking of diseases as if they had a real existence apart from the men, women, and children who suffer from them; and to impress the lesson that the real object of medicine is not the application of science to a diseased body but the relief of human suffering. The purpose is excellent; the task is a little difficult to fulfil. Sometimes the human side of the story is overweighted by technical detail; sometimes the picture is too sombre. I liked best the story of the eccentric behaviour of Mr. Swindlethorpe, the managing director who had G.P.I. It has a happy ending, for he responded to intensive treatment with penicillin.

Medical readers will appreciate this excursion of a distinguished physician into the realms of fiction. Miss Treadgold's illustrations are apt and amusing.

ARTHUR S. MACNALTY.

Until now Canada has had no medical directory of its own, its physicians and surgeons having been listed in the unwieldy *American Medical Directory*, which last appeared five years ago. Now the first *Canadian Medical Directory* has appeared, appropriately enough a few months before the joint meeting of the British and Canadian Medical Associations, and it will be particularly useful to those concerned with that meeting. The directory has three divisions—an alphabetical listing of doctors; a geographical listing by province and town; and a section containing general information on medical societies, departments of health, universities, journals, etc. The arrangement owes something to our own *Medical Directory*, although entries are not so informative. The *Canadian Medical Directory* is issued by Current Publications Ltd., 9, Duke Street, Toronto, 2, Canada, and costs $7.

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ACUTE RHEUMATIC FEVER IN CHILDREN

Of unique historical interest, the article in our opening pages this week is a report of the first international clinical trial to be carried out. The study was sponsored by the Rheumatic Fever Working Party of the Medical Research Council of Britain and the Subcommittee of Principal Investigators of the American Council on Rheumatic Fever and Congenital Heart Disease, American Heart Association. It was designed to test the relative efficacy of A.C.T.H., cortisone, and aspirin in the treatment of acute rheumatic fever, with reference not only to the relief of acute symptoms but to the prevention of cardiac damage.

Nearly six years have passed since Hench and his colleagues[1] reported their observations on three adolescent patients, suffering with acute rheumatic fever, to whom they administered adrenal cortical hormone. Compound E (Kendall) acetate was given by intramuscular injection, the dose being 200 mg. daily for several days, and then 100 mg. daily for a few days more. The immediate results were gratifying, and the paper is well worthy of study not only for its historical interest but also as a model of careful clinical observation and scientific wisdom. Many subsequent reports, such as that of E. N. Chamberlain, J. D. Hay, and D. M. Freeman,[2] have borne witness to the efficacy of adrenal hormone during the acute stage of rheumatic infection. But is it a better treatment than salicylates, and does it possess the additional advantage of preventing progressive and permanent cardiac damage ?

In all, 505 children aged under 16 were admitted to the study (242 in the United Kingdom and 263 in the U.S.A. and Canada) ; 5 were subsequently excluded. The remaining 500 were allocated by random sampling methods to the three treatment groups, subdivided according to lapse of time between onset of symptoms and beginning of treatment. The results of treating 497 patients were finally analysed. Diagnostic criteria and details of treatment should be consulted in the report, and the reader will be impressed by the great care taken to enable reliable conclusions to be drawn. Treatment was given during a six-weeks period, and at the same time the dietary intake of sodium was restricted to less than 2 g. per day for all patients, to minimize salt retention in hormone-treated patients and to maintain comparability among the three treatment groups.

Attempts were made to prevent recurrent attacks of rheumatic fever by giving penicillin during the first two weeks of treatment, and sulphadiazine from the fourteenth day onwards. Follow-up data (with special reference to rheumatic heart disease) were obtained at intervals during the succeeding year. The investigation continues, and a final determination of each child's cardiac state will be awaited with interest. But several important conclusions emerge from the results to date. There is no evidence that rheumatic fever in childhood can invariably be terminated by any of the three treatments used ; hormone therapy controls the acute manifestations more quickly than does aspirin, but there is a greater tendency for them to reappear for a short time at the end of treatment ; and at the end of one year there was nothing to choose between the three groups in respect of cardiac state. This last conclusion is disappointing, though there is still the possibility that a longer survey of these patients may show some advantage to lie with the hormone-treated group. But it seems unlikely that this treatment will be shown to have any spectacular effect in protecting the heart, and the challenge of rheumatic carditis must still be met mainly by preventive measures.

In the Harveian Oration given to the Royal College of Physicians in 1945 Sir John Parkinson[3] estimated that about 16,000 people were dying annually of rheumatic heart disease, and that at least 200,000 people between the ages of 18 and 41 were at that time suffering from heart disease, mostly rheumatic. It is well known that the incidence of rheumatic infection has been waning for some years, but we should not assume that this decline will necessarily continue, and some districts have recently reported a local increase. At present about 4,000 to 5,000 new cases occur annually in England and Wales in the age-group 5 to 14 years, and to this figure must be added the frequent cases of relapse—an increasing threat to the heart. Unfortunately, from the point of view of effective prophylaxis, mystery still surrounds the essential nature of rheumatic infection. Both genetic and infective factors have to be considered,[4] and many workers, including Bruce Perry[5] and Ryle[6] have emphasized the significance of social conditions in the child's environment. Family income,

[1] Hench, P. S., *et al.*, *Proc. Mayo Clin.*, 1949, **24**, 277.
[2] Chamberlain, E. N., *et al.*, *British Medical Journal*, 1952, **1**, 1145.
[3] Parkinson, J., *Lancet*, 1945, **2**, 657.
[4] Bradley, W. H., *Proc. roy. Soc. Med.*, 1950, **43**, 979.
[5] Perry, C. B., *Bristol Med.-chir. J.*, 1944, **61**, 1.
[6] Ryle, J. A., *J. roy. Sanit. Inst.*, 1946, **66**, 277.
[7] *Courrier*, 1954, **4**, 357.
[8] Perry, C. B., and Gillespie, W. A., *British Medical Journal*, 1954, **2**, 729.
[9] Stollerman, G. H., *Amer. J. Med.*, 1954, **17**, 757.
[10] Catanzaro, F. J., *et al.*, ibid., 1954, **17**, 749.

nutritional standards, overcrowding, and ventilation all seem to bear a relationship to the prevalence of rheumatic infection, and when a single factor is sought that might be common to these possible influences the most likely conclusion is that it lies in infection (especially of the nose and throat) with group A β-haemolytic streptococci.

Claims have been made that the incidence of rheumatic infection can be lessened by effective treatment of these streptococcal infections during the acute phase, both in the primary attack and in relapses, and by sterilizing the upper respiratory passages of carriers. Sulphonamides were at first used, but sometimes they caused toxic symptoms, and the micro-organism developed resistance. Penicillin was found to be free of these disadvantages and has been administered, apparently with success, by mouth and by injection. The prophylactic dose of penicillin, when given by mouth, is 200,000 units three times daily on an empty stomach.[7] But this treatment must be given over a long period, and the patient's forgetfulness may result in intermittent dosage. Bruce Perry and W. A. Gillespie[8] have shown that a monthly injection of benzathine penicillin gives a prophylactic blood level and eliminates group A haemolytic streptococci from the throat. G. H. Stollerman[9] and F. J. Catanzaro *et al.*[10] seem to be in general agreement, and they stress the importance of effective penicillin treatment of the primary pharyngeal infection within ten days of its onset.

Acute rheumatic infection in childhood is still a dangerous menace demanding the continued attention of paediatricians, public health officers, and laboratory workers.

OPERATIVE TREATMENT OF AORTIC ANEURYSMS

It is now agreed that surgical treatment should be considered when the diagnosis of aneurysm of the aorta is made. The prognosis is grave and medical treatment ineffective.[1] The palliative manœuvre of wiring—to induce a clot formation within the aneurysm—by passing into the lumen a length of wire, either as a continuous coil or as a Colt's wisp,[2] is often effective in relieving pain and may retard the enlargement of the aneurysm and improve the prognosis: it can only be done for saccular aneurysms with a well-formed neck, where thrombosis will not involve the main aortic blood stream. Wiring has been practised for many years, but never extensively. A small number of radical operations have now been carried out both for saccular aneurysms and for fusiform aneurysms not involving the proximal aortic arch above the origin of the left common carotid artery. Saccular aneurysms can be excised and the aorta repaired if a clamp can be placed tangentially across the neck without occluding the aortic lumen, so as to allow lateral suture. Fusiform aneurysms can usually be treated only by grafting, a preserved homograft being used to bridge the gap left after excision.

Aortic grafting was first done for cases of coarctation where the segment which had to be resected was too long to allow direct end-to-end suture.[3] In coarctation an extensive collateral circulation develops in response to the congenital obstruction of the aorta: clamping the aorta during the operation has little effect on the blood flow to the lower part of the body, and ischaemic effects are very unusual. These operations showed that grafting a large artery was practicable and helped to establish the principles described in a recent leading article in this *Journal*.[4] Thrombosis and rupture of an anastomosis or of the graft are uncommon complications after operative treatment of a coarctation, and it now appears that this will also hold good for grafts applied after excision of aneurysms which may be of a traumatic, arteriosclerotic, or syphilitic origin. For lesions of the lower abdominal aorta, beyond the origin of the renal arteries, the necessary temporary interruption of the aortic blood stream does not usually lead to circulatory disorders. Clamping the aorta above this level for more than a short time leads to irreversible ischaemic effects on various tissues. The most susceptible organ is the spinal cord and its cauda equina, and the kidneys come next. An interruption of blood flow for ten minutes may lead to permanent paraplegia. The exact danger period is not at present accurately known: it depends on age, being considerably longer in children, and on the degree of general arterial disease present. It probably usually lies between fifteen and forty-five minutes. A grafting operation entails clamping the aorta at two levels, above and below the aneurysm. After it has been excised two anastomoses must be made between aorta and the two ends of the graft, which may well take a considerably longer time than can be tolerated.

There are two ways in which the dangers of ischaemia can be avoided. First, a by-pass can be arranged so as to allow the aortic flow to continue throughout the operation. This adds considerably to the technical difficulties, but perhaps with increasing experience a satisfactory method will be devised. Alternatively the oxygen demands of the tissues

[1] Borrie, J., and Griffin, S. G., *Thorax*, 1950, **5**, 293.
[2] *Quart. J. Med.*, 1927, **20**, 331.
[3] Gross, R. E., *et al.*, *Surg. Gynec. Obstet.*, 1949, **88**, 689.
[4] *British Medical Journal*, 1954, **2**, 218.
[5] Churchill-Davidson, H. C., McMillan, I. K. R., Melrose, D. G., and Lynn, R. B., *Lancet*, 1953, **2**, 1011.
[6] *Surgery*, 1954, **36**, 33.
[7] *J. Amer. med. Ass.*, 1954, **155**, 1398.

beyond the level of aortic occlusion can be reduced by lowering the body temperature. It has been shown experimentally that as the temperature falls oxygen consumption is progressively reduced, being about one-third the normal at 27° C.[5]: the cells can obtain enough oxygen for their basal needs without any arterial blood flow for at least a proportionately increased period. Hypothermia thus considerably prolongs the period for which ischaemia can be tolerated, and it allows the thoracic aorta to be clamped for long enough to carry out the necessary operation without haste.

The theoretical advantages of hypothermia in avoiding ischaemic complications after clamping the aorta have been confirmed by experiments carried out on dogs and reported by De Bakey and his colleagues[6] from Texas. They clamped the aorta at various levels. Many of the animals died in both the control group operated on at normal temperatures and in the group of hypothermic animals. But of the control animals which survived 65% had paraplegia, whereas none of the surviving animals in the hypothermic group had this complication. De Bakey and Cooley[7] have also recently reported a successful resection and grafting operation for a traumatic aneurysm of the distal aortic arch in a man aged 31. At a first operation a saccular aneurysm was excised and lateral suture performed. An accompanying fusiform aneurysm then increased in size and caused symptoms necessitating a second operation. This was done under hypothermia, the temperature being reduced to about 27° C. by surface cooling with a refrigerating blanket. The aorta was clamped for one hour, while a 9-cm. defect left after excision of the aneurysm was replaced by a homograft preserved in tyrode solution. The patient made an uneventful recovery, after evacuation of a haemothorax, and at no time were there any symptoms of spinal-cord damage.

SEPTIC INJURIES IN INDUSTRY

Most of the injuries requiring treatment in the factory surgery are small lacerations and puncture wounds, and the majority of them affect the hands. These common cuts usually heal uneventfully and do not cause any great inconvenience to the worker, nor do they result in loss of working time. But a few of them become septic, and these are apt to give more trouble. As a cause of losing three or more days' working time, sepsis accounts for about 7% of notifiable factory accidents,[1] though the conditions of notification make it likely that the real figure is rather more than this. Since the war there seems to have been a decline both in the total numbers of septic injuries and in the proportion which they bear to total notifiable accidents. This decrease has been found in all types of industry, though some—particularly those concerned with metal working—continue to have a much higher incidence than the rest.

The recent study by Wilkes[2] gives further evidence of the continuing social cost of these septic injuries. Among 151 patients with infections of the hands, the usual amount of time lost was from two to four weeks, and the net loss of earnings for each man averaged about £3 10s. a week. The actual cost to the community must be several times this figure: apart from the further expenses of sickness and injury benefit with no productive return there are the costs of medical treatment, and there are further losses, though difficult to estimate, due to disturbance of team work.

The cases of sepsis as they come to the surgery divide themselves into two groups: those septic when first seen and those which become septic under treatment. The first group includes the majority of finger-pulp infections and paronychias, and because of the peculiarities of the local anatomy they present special problems of treatment and prevention. The causative organisms are most often penicillin-sensitive staphylococci. It might have been expected that penicillin-resistant forms would by now be common, but the findings of Harrison *et al.*[3] and Robins[4] suggest that they are not. Though more recent bacteriological studies are not available, it seems likely that such infections which arise away from hospitals and the common use of penicillin are caused by organisms which are still penicillin-sensitive. A combination of careful surgery and systemic penicillin has almost certainly contributed to the reduction of lost time due to sepsis, and complications such as tendon-sheath infections with their resulting disabilities are now increasingly rare.

If patients with these septic lesions are questioned, a history of some injury can often be elicited. Commonly mentioned are knocks against pieces of metal, splinters, or the edges of hand tools. Many of the patients frequently have such minor injuries in the course of their work, and it is difficult to attribute with certainty the septic condition to any particular one. Radiography of metal workers' fingers will often show the presence of many other splinters of "swarf" in the tissues than the one which is believed to be the cause of the sepsis. Of the patients

[1] *Ministry of Labour and National Service, Annual Report of the Chief Inspector of Factories for the year* 1952, 1954, H.M.S.O., London.
[2] *Brit. J. industr. Med.*, 1954, **11**, 269.
[3] *Lancet*, 1949, **1**, 425.
[4] *J. Bone Jt Surg.*, 1952, **34-B**, 567.
[5] *Brit. J. industr. Med.*, 1945, **2**, 217.
[6] *Spec. Rep. Ser. med. Res. Coun. (Lond.)*, No. 266. 1949.
[7] Gissane, W., *et al.*, *Brit. J. industr. Med.*, 1944, **1**, 90.
[8] Bull, J. P., *et al.*, *Lancet*, 1948, **2**, 213.
[9] Schilling, R. S. F., *et al.*, ibid., 1950, **1**, 293.

with septic lesions studied by Wilkes at the Newcastle Hand Clinic, 30% had no memory of any injury, and it is possible that in some cases organisms enter the tissues through minor cracks or even the normal sweat and sebaceous glands. The suggestive evidence presented in this study that a "run down" state of health commonly preceded the sepsis would fit in with this implication of reduced resistance to infection. Some of the patients have septic lesions such as boils elsewhere on the body which might be the source of heavy contamination of the skin with *Staph. aureus*, though about 20% of normal people having no such lesion carry these organisms on their skin. In these circumstances the prevention of all cases of sepsis is probably not attainable. In some factories earlier and better treatment of minor injuries would doubtless be an improvement, but in those with good facilities a stage is soon reached when it is not feasible for every minor wound to be treated. Williams and Capel[5] found that about 7% of engineering workers injured themselves every day, and Wilkes quotes a workman: "If I reported everything I might just as well sit in the accident room all day." Two general lines of preventive action seem promising: improvement in methods of working, so that swarf and sharp edges are kept away from the workers' hands; and good washing facilities and changes of clothing should reduce the load of infection of the skin and hence the proportion of injuries becoming septic.

The second clinical type of sepsis, that occurring during treatment of an open wound, may also be due to staphylococci, but the more severe examples are streptococcal. The development of sepsis in such wounds is relatively rare, but the fact that it occurs at all means that current methods of treatment could be improved. These infections may occur at the time of dressing, and the studies reviewed by Williams and Miles[6] give a clear lead to better techniques. A carefully planned routine of treatment incorporating a no-touch technique is necessary, and this is made easier if the lay-out of the dressing station is appropriately designed.[7] Infection occurring between treatment times may sometimes be due to interference by the patient, but it must sometimes be attributed to the present lack of a really satisfactory surgical dressing which will stand the hazards of normal industrial work. Such a dressing needs to be bacteria-proof; it should be permeable to water vapour so as to avoid sogginess of the skin; it should be resistant to water, oil, and common industrial solvents; and it must remain in place when in contact with these materials during the patient's work. Attempts at such a dressing have already been made,[8 9] but further development on these lines is needed.

CHILBLAINS

Damp cold is the most troublesome kind of cold weather for those who are susceptible to perniosis or erythema pernio, commonly known as chilblains. Lewis[1] found that the vascular responses of these people were normal if their limbs started by being warm, but if they were cold (as they usually are) there was evidence of abnormally high vascular tone and an increased readiness to develop arteriolar spasm. Together with this spasm of arterioles a dilatation of other blood vessels can be seen, leading eventually to histological appearance of chronic inflammation, fat necrosis, and obliterative endarteritis. Why damp but not dry cold should be to blame is not clear, but the geographical distribution of chilblains, as quoted by Mitchell Heggs,[2] leaves little doubt of it. Our climate must be accountable for the high incidence in Britain. Adolescents suffer most, particularly young women whose legs are poorly protected; fresh cases are rare after the age of 40. So-called erythrocyanosis crurum, dermatitis hiemalis, and nodular vasculitis are conditions which affect mainly the same group and appear to have the same aetiology: it is doubtful, therefore, if anything is gained by preserving their separate dermatological identities. R. B. Lynn[3] suggests that all these manifestations of one pathological process should take the simple name "chilblains." There are many who will be less ready to agree that erythema induratum (Bazin's disease) is not, after all, of tuberculous origin but attributable like the rest to cold.

Lynn emphasizes the distinction between acute and chronic chilblains. Acute chilblains, even if they develop vesicles which rupture, usually clear up in a few days whatever treatment is applied, provided that exposure to cold is not repeated. Susceptibility to acute chilblains often seems to diminish as the patient grows older. A seasonal nuisance, they can usually be avoided if a good diet and sufficient exercise are taken, and above all if the victim consents to be sensibly clothed and shod. But neglect of these rules later in life, or prolonged and repeated exposures to cold from the first in people who are exceptionally prone to chilblains, may lead to changes which persist. Such chronic chilblains, using the term to include all the various clinical appearances, must be regarded as a further stage in the disorder—the pathological changes having become irreversible. Limbs which have been affected by neurological diseases like anterior poliomyelitis are particularly susceptible, which suggests that there may be several predisposing factors in the development of chronic chilblains. Tuberculosis does not seem to be one of these, save in so far as it may affect the general resistance. The sufferers are often young or middle-aged women with stout limbs and thick ankles. Commonly there is symmetrical involvement of the limbs, especially in the lower third of the legs, but sometimes the condition extends to the knees and thighs. Persistent blotchy, reddish-purple discolorations progress to large, swollen, raised lesions which even the coming

[1] *British Medical Journal*, 1941, **2**, 837.
[2] Mitchell Heggs, G. B., in *Modern Practice in Dermatology*, 1950, London.
[3] *Surg. Gynec. Obstet.*, 1954, **99**, 720.

of warm weather will not disperse. Later still the raised nodular lesions ulcerate. The ulcers may heal slowly to form permanently pigmented scars, but are liable to break down finally and coalesce to become large, indolent, open lesions.

In the treatment of chilblains calcium, vitamins, and ultraviolet light have had, and still have, their adherents as general measures. Local applications in great variety have been tried, including emollients, antipruritics, and counter-irritants; but their very number testifies to their slight effectiveness, and the main attack on chilblains should not be local. The basic disorder is arteriolar spasm, and it is rational to use nicotinic acid or tolazoline to offset it. Sympathectomy was suggested almost twenty years ago. This also is a rational form of treatment, though some may think it too drastic. Yet in their chronic form chilblains may cause pain, distress, and disfigurement severe enough to warrant drastic steps. Lynn reports that there has been no recurrence of ulceration on 40 limbs (of 25 patients) after lumbar sympathectomy. But the crux of the matter is prevention. Women may have to choose between the disfigurement of chronic chilblains and the less permanent embarrassment of wearing wool.

"SLUM SICKNESS"

An attempt has recently been made in Glasgow to discover the extent to which the removal of families from slums to new houses has had a beneficial effect on their health, and on social behaviour as measured by juvenile crime.[1] For this purpose the circumstances of 388 families living in old slum property were studied, together with those of 718 families who had formerly lived in old slum houses but had been rehoused for periods ranging from ten to twenty-seven years. It was hoped at the outset of the survey to superimpose the pictures thus obtained of these two sets of families and study the contrasts, but it unfortunately proved impossible to do so, mainly because the families which had been rehoused were much older than those in the slums. Nevertheless, some interesting facts emerged, which deserve further consideration.

In the first place the comparative youth of the slum families is interesting, because it shows that the slum community which was investigated was the creation of the housing shortage; young people were unable, it seems, to find any accommodation other than in the slums to live in during the early stages of their married life. Poverty (except in the case of old people) could be disregarded as an influence driving them there, for more of the wage earners in the slums than formerly are hard-working, often skilled or semi-skilled operatives in regular employment. Indeed, the proportion of parents classified as in good health was higher in the slums than in the new houses, the reason no doubt being the differences in age between the two groups. In other respects few contrasts were found between the slum families and those which had been rehoused. The feeding habits of the rehoused families, for instance, showed no improvement on those of the slum population, and deaths of children varied little between the two groups. Delinquency among the boys who were members of rehoused families, again, was "very similar" to that experienced among young people still living in slums. As previous researches had indicated, it was found to be "much in excess" of that which prevailed even among boys who had left school at the earliest permitted age. This may demonstrate that the social consequences of slum life are more harmful to young people than its physical effects.

The conclusion drawn by the authors from this argument is, they think, abundantly clear: "many slum families require a great deal of help and encouragement to make the transition from the slums to a new life," for the evidence "shows again that the eradication of slum sickness does not come with the mere erection of new houses." There is therefore obviously room for a more intensive study of the forms which this "help and encouragement" takes, in order to discover which of them is the most effective; this would require a general survey of the impact of all the social services, from health visiting to housing management, on the members of rehoused families.

One reassuring point emerges from the investigation. The work carried out by Dr. McGonigle in Stockton-on-Tees in 1933 demonstrated that the effect of moving slum dwellers to new houses might have harmful consequences, so far as their health was concerned, because increased rents might leave them with less to spend on food. In Glasgow, however, it was found that the redistribution of purchasing power has freed the rehoused families from economic pressures of this kind. On the contrary, there was an evident need "for the provision of more new houses, particularly to permit removal from the perils of a slum environment of young families at present driven to live there though they could well afford to pay a reasonable rent and would willingly do so."

[1] Ferguson, T., and Pettigrew, Mary, "A Study of 388 Families Living in Old Slum Houses" and "A Study of 718 Families Rehoused for Upwards of Ten Years." *Glasg. med. J.*, August, 1954, **35**, 169.

FLAVOURED MILK

Milk to which various "fruity" flavours have been added is now being sold in increasing quantities. The flavours are mainly synthetic, but concentrated flavouring essences prepared from natural fruit are also being used on a small scale. Promotion of milk sales is the obvious purpose of these flavours; and "Drink More Milk" is a slogan which the medical profession can fully support provided there is no risk to the health of the consumer. As the law stands, however, flavoured milk escapes the provisions in the Food and Drugs (Milk, Dairies and Artificial Cream) Act, 1950, which limit the sale of milk "in specified areas" (mainly the large urban areas) to tuberculin-tested, pasteurized, and sterilized milk. This is a loophole in public health legislation that might well be closed. Fortunately the milk industry itself is aware of the risk, to which attention has already been drawn by the chief chemist[1] of the Milk Marketing Board and by the general secretary[2] of the National Dairymen's Association. Both strongly recommend that

[1] Provan, A. L., *Milk Industry*, January, 1955, p. 37.
[2] O'Neill, P., ibid., January, 1955, p. 41.

milk should be heat-treated after addition of the syrup which carries the concentrated flavours. This authoritative advice should certainly be heeded by dairymen, whether the law is amended or not. The nutritive value of flavoured milk should not differ appreciably from that of ordinary milk, but some mothers may see in these flavoured milks, especially if they have an orange flavour, a convenient means of giving their babies at one and the same time its proper feeds of milk and of vitamin C. Such notions should be dispelled.

CARRIER STATE IN VIRAL HEPATITIS

Experience with viral hepatitis in the second world war led to the differentiation of two closely related forms of the disease—infectious and serum hepatitis—but the lack of a practicable experimental approach has prevented the exact relationship between the two forms from being determined.[1] Reviewing the present state of knowledge on viral hepatitis, a W.H.O. committee[2] drew attention to some of the pressing problems needing clarification, of which the duration of the carrier state in both types was an important item. Recently three reports of preliminary findings on this aspect have appeared, based on the inoculation of human volunteers under carefully controlled conditions.[3–5]

In infectious hepatitis the virus (IH or virus A) is present in the blood for a short time before and during the acute phase of the disease and for longer periods in the gastro-intestinal tract.[2] The normal duration of faecal excretion is probably short, but the existence of faecal carriers has been considered a probable explanation of the smouldering endemic infection encountered in institutions.[6] Investigations carried out by Stokes and his colleagues[3] on two young children from an orphanage where hepatitis had been endemic for a number of years[6] established that both had chronic active hepatitis without jaundice and both were faecal carriers of virus A, in one case for six months and in the other for fifteen months after the initial illness.

In serum hepatitis the virus (SH or virus B) has been demonstrated unequivocally only in the blood, in which it may persist for long periods. Just how long in the average case is not known, but three apparently healthy donors also investigated by Stokes and his colleagues[3] were found to have virus B in their blood for at least 5½, 3, and 1½ years respectively. One donor appeared to be a true "silent carrier" for at least three years, in that she was symptomless and liver-function tests were within normal limits. This patient's newborn infant developed jaundice at the age of 2 months and succumbed to it. Virus B was recovered from the blood of mother and child by inoculation of human volunteers. Transplacental infection and the existence of silent carriers may help to explain some of the epidemiological aspects of virus B infection.

As both viruses are present in the blood, hepatitis can result from parenteral inoculation with either virus A or virus B if blood is collected during the viraemic phase, though it more often follows the longer incubation usually associated with virus B. In two further reports[4 5] on viral hepatitis in blood donors it appears that 28–42% may have been due to virus A if the criterion of distinction is the length of the incubation period. Differentiation on this basis is clearly difficult but is of some practical significance, as there is more chance of type A viral hepatitis being controlled with gamma globulin.

None of the donors referred to in these reports gave a history of jaundice; a few admitted to vague non-specific illnesses, and more showed abnormal results in liver-function tests. These findings are worth bearing in mind in selecting blood donors[7] and emphasize the need for a laboratory test for the detection of healthy carriers of either virus.

ANAESTHESIA AND THE COMMON COLD

Medicine is plagued by myth and mumpsimus,[1] the extent of which was only barely indicated in J. R. Forbes's stimulating and entertaining paper.[2] Now George Ellis[3] suggests that perhaps he might have included as an example of mumpsimus the belief that anaesthesia is contraindicated in the presence of the common cold. However, even Ellis would agree it would probably be going too far to say there is no foundation whatever for the belief that anaesthesia is better avoided in these circumstances. The hundred years or so of world-wide experience of anaesthesia has shown that an anaesthetic may well exacerbate an upper respiratory infection and that more serious chest complications may follow. Nevertheless, Ellis points out, there is little worthwhile factual evidence on this matter. No one will disagree with him that if the operation is urgent then the common cold can be ignored; equally so, that an operation which is necessary for a patient's livelihood or peace of mind should not be postponed. He carefully points out, however, that "it is all too likely that the patient will acquire a nasty hacking cough and that therefore abdominal operations, including those for hernia, should be postponed." Operations on the respiratory tract itself and those inside the chest are better not performed. But Ellis does maintain that a whole host of operations of less gravity, and outside these regions, could be carried out with little increased risk in the presence of a common cold. In view of the current bed shortage and long waiting-lists, Ellis's opinions deserve the closest consideration. They may well be treated with a little reserve and should not be construed into meaning that the presence of a common cold indicates an anaesthetic. This refreshing paper is a worthy addition to the literature on mumpsimus in medicine.

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EMERGENCIES IN GENERAL PRACTICE

ATTEMPTED SUICIDE

BY

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A patient's suicidal attempt commonly takes both his relatives and his doctor by surprise. In this emergency the doctor's first duty is to conserve the patient's life, by administering whatever first aid is necessary for the injuries sustained, and by arranging without delay for the patient's further physical and psychological care and treatment. This duty takes precedence, of course, over any detailed investigation of the causes and circumstances of the attempt. Where possible, immediate admission to the mental observation ward of a general hospital is the ideal arrangement. Even if the individual has not sustained serious hurt and the situation appears less urgent to his relatives, it is usually advisable to insist that he goes into hospital. The most skilled medical and surgical care is available there for the treatment of injuries: also a breathing space is obtained, during which the situation may be calmly assessed by everyone concerned. The patient should always be kept under observation for at least a few days. He must be safeguarded from further self-injury, his relaxation and sleep must be ensured by sedatives, a detailed assessment of his mental and physical state must be made, the relatives interviewed, and both the individual and the social aspects of the situation fully considered. Usually a proper decision about his future can be taken within two weeks.

All this calls for such a specialized investigation that the help of a psychiatrist should be enlisted as soon as possible, whether or not the patient has been admitted to a general hospital. Where the practitioner is unsupported by a general hospital or psychiatric advice, he will have to rely more on his first estimation of the seriousness of the attempt (see below) in deciding whether or not to arrange prompt admission to a mental hospital. Mental hospital admission is most often required for those suffering from depressive, schizophrenic and paranoid psychoses, and more often for those past middle age than for younger individuals. It is necessary for most of those aged 60 years or over. If the individual's progress cannot be adequately watched and safeguarded at home, mental hospital or other in-patient care is essential. Admission to a mental hospital should not, however, be made the rule: of those who are admitted initially for a short period to a general hospital, about one-half may be discharged home reasonably safely. Those who go to a mental hospital will usually do so as voluntary patients. Psychiatric out-patient treatment is required for many others.

To discharge from observation an individual who has attempted suicide, just as soon as he is physically fit, is malpractice. Sometimes the patient is asked first to promise that he will not attempt suicide again. This promise, if given, is usually valueless. It may reassure the doctor but it does nothing to safeguard the patient, who can no more control his self-destructive impulses than the sufferer from an acute appendicitis his pain.

How Serious was the Attempt?

The determination behind a suicidal attempt may be very difficult to measure and cannot be judged by any one criterion. It is not profitable to draw a sharp distinction between real suicidal attempts and suicidal gestures. It is better to err on the safe side, which is to consider a gesture a real attempt and to treat it as such. After middle life suicidal gestures are uncommon; in old age they are exceptional.

If the individual has injured himself seriously, or has jumped from a height, or has attempted to hang or drown or shoot himself, there can be little doubt that he intended to take his life. The more bizarre the method used, the more likely is it that the individual is seriously mentally ill. Those who have chosen a solitary place, and those who have used more than one method, are likely to have been in earnest.

That the attempt was feeble in execution does not, however, necessarily mean that the intention was feeble. If the individual has not taken a gross overdose of drugs, or has attempted gassing with the windows open, or has made only a few superficial cuts on his wrists or throat, it is sometimes immediately concluded that he was not serious. But a psychotic patient may make a poor attempt: his agitation or retardation may cloud his judgment and render his hands impotent.

It is of great importance to find out if the individual who has made the attempt has recently appeared nervously ill. If he has not appeared to be ill, especially if he is of chronically unstable temperament, and if the act has been an obvious response to some quarrel or frustration and is described by the actor as done on the spur of the moment, then one may usually conclude that the immediate danger has passed, particularly if the actor himself has become calm again. But there are exceptions here too: the young schizophrenic, hardly recognized to be unwell, may act with great impulsiveness.

Unfortunately one cannot accept at its face value the patient's own estimation of his act, but one must correlate his statement with the rest of the evidence. Not infrequently a suicidal individual denies his suicidal intentions after the act, out of fear of police action or the reproaches of relatives, or to get another opportunity to complete the act. On the other hand, an admission of suicidal intent is usually to be believed. A farewell letter is usually of serious import, and its contents may throw light on the motives which prompted the attempt. Inquiry should always be made whether or not the individual left any communication, since such letters are often suppressed or quickly destroyed by relatives.

The most difficult cases to assess are often those in which the suicidal attempt has been made at home and the method has been barbiturate poisoning. The individual may assert that all he wanted was a long sleep. This statement should not be readily accepted. Some suicidal individuals will deny vehemently that suicide was their intention. The story may be given that the drugs were at the bedside, that the patient took two perhaps, then two more, and when drowsy more still. Such an accident, leading to prolonged and deep unconsciousness, is rare. The story, which relatives are only too glad to accept, is usually a cloak for a suicidal attempt.

Attempts made when the individual is under the influence of alcohol are also difficult to assess. While it is true that certain suicidal attempts are made under the influence of alcohol which would not have been made in a state of sobriety, alcohol may release a serious suicidal trend; it may also interfere with its consummation. It may be very difficult in these cases to know how prolonged was the oblivion sought. Perhaps two-thirds of such attempts are to be judged serious.

That the attempt was dramatic does not necessarily mean that it was not serious. A serious attempt may be dressed up for and executed publicly. The sufferer from a depressive psychosis may wish to demonstrate to others the extent of his wickedness and his self-punishment: while the aggressive psychopath, venting a murderous spite upon himself, may at the same time court a posthumous publicity by which relatives will suffer.

More men than women commit suicide, and men more often use active and violent methods. These generalizations, though true, hardly help one with the individual case.

Could it Have Been Prevented?

After such a distressing emergency has arisen, one is prompted to ask, could it have been foreseen and forestalled? While it is perhaps doubtful if the really determined individual can often be deviated from his intention, it must be admitted that preventable suicides do occur. They occur because either the doctor or the relatives or both feel sure that, knowing the patient to have been a decent and trustworthy person, a suicidal attempt was not to be expected. But suicide is no respecter of persons.

Almost any nervous or mental illness, at any age, may lead to a suicidal attempt. Suicide is thought of particularly in relation to depressive psychoses, but it is a mistake to consider it as limited to them. It may be a symptom of any psychosis where there is emotional disturbance. It cannot be ruled out in neurotic reactions. It may be the panic response to a sudden crisis of disablement or bereavement, for example, or to a threat of loss of liberty or reputation, or to the self-discovery of homosexual trends. It is the typically exaggerated response to frustration of that large group of temperamentally unstable people which includes the psychopaths and a certain number of epileptics and mental defectives.

The emphasis must be on the early diagnosis of nervous and mental instability, and on treatment and protection at the earliest possible stage. If the risk of suicide is thought of, it is much more likely to be recognized. To appreciate, even approximately, the degree of risk one must get to know the patient well, must give him time to speak freely about his problems, and must exercise great delicacy in questioning when trying to sense the dangers of his situation. At a single interview it is usually possible to give the depressed patient a feeling of confidence that he is understood; and if he has admitted to despondency he may then be asked if he has had any morbid thoughts or at any time felt discouraged or even hopeless about his future or the outcome of his illness. He must be gently assisted, never forced, to reveal further his emotional state. Any disclosure of suicidal thoughts should be taken seriously. When a patient has spoken of suicidal thoughts it is advisable always to reassure him that these are usual symptoms of a depressive illness, that they are not evidence of sinfulness, and that they will disappear as the illness lifts.

On physical examination scars on the neck and across the fronts of the wrists, which might indicate a previous suicidal attempt, should be noted. There are other features of the patient's history and symptomatology which will point to a particular need for vigilance.

Warning Signs

One still often hears it said that those who talk of suicide to other people do not commit it. This is a false and dangerous belief. At least one-third of those who attempt suicide have threatened suicide. Such threats should therefore never be ignored but should be evaluated carefully in the setting of the type of abnormal reaction and all the individual circumstances. Suicidal threats are not only warnings often of an impending attempt, but cries for help.

If a history of a suicidal attempt in a previous illness is obtained it increases the risk in the present illness. In the case of the manic-depressive, the fact that previous depressions have not been associated with a suicidal attempt may give one a feeling of greater security about the risk in the present illness, but it does not exclude this risk. Neither does one suicidal attempt in a depressive illness eliminate the possibility of further attempts in that illness.

A family history of suicide is significant, and there may be a family mode of committing suicide. A living person may come to identify himself with someone who is dead. If he becomes depressed he may wish to rejoin that person; and if he says so, this is usually to be construed as a suicidal threat. If the individual identified with has himself committed suicide, the risk of a duplicate suicide is materially increased.

There is some evidence also that the history of a "broken home" in childhood is correlated with an increased suicidal risk.

Depression and insomnia are the usual symptomatic precursors of a suicidal attempt. All depressions carry a suicidal risk, whether they have clear precipitants—for example, bereavement, financial ruin—or come out of the blue. The risk is often greatest in the early stages of the illness, and again in convalescence. This unexpected and almost paradoxical risk in convalescence is often forgotten. Depressions associated with retardation are less dangerous than tense, agitated depressions. Any individual past middle-life, who presents a picture of persistent anxiety and who has not previously had neurotic symptoms, should be suspected of suffering from an early involutional melancholia and precautions against suicide should be taken without delay. Particularly dangerous are those who blame themselves, who express feelings of intense shame and guilt and failure, and who say that their continued existence would be burdensome for those they love. The obviously very depressed individual who denies having had thoughts of suicide should on principle be disbelieved: he may be determined to be unhindered. Those who say that they are too cowardly to carry out the act may do it successfully.

Insomnia, Fear, and Loneliness

In general the greater the concern about insomnia, the greater the suicidal risk. The patient may assert that he is certain that lack of sleep is doing irreparable damage to his brain. Though he may sleep for some hours, he may declare that he has not slept at all; if one just dismisses the statement as untrue, one will miss its significance as a danger signal. The psychotically depressed individual often wakens at an early hour of the morning, and is most ill then. A suicidal attempt is often prefaced by a sleepless night.

Severe hypochondriasis in a depressive setting is also a significant complaint, particularly if it is focused on a single organ or part of the body and is accompanied by a phobia of disabling or fatal disease—for example, tuberculosis, heart disease, cancer. The fear of insanity is very common, often associated with intense feelings of tension and head pains, so that the patient feels that something is about to snap in his head. Venereophobia also, accompanied by depression and agitation, must be viewed very seriously. The individual's feelings of great guilt and contamination may urge him to attempt suicide even before the result of a blood test becomes available. Perhaps the most potent fear of all is the dread of the unknown.

Of all the reality fears which may precipitate serious suicidal attempts, the prospect of entering a mental hospital is one of the most noteworthy. The period during which arrangements are being made for a depressed patient to

enter a mental hospital, if the patient has got to know what is planned, is a period of real danger, during which he must not be left unattended.

In a depression, fears of losing control and of hurting or killing others, and actual attacks upon others, particularly if this behaviour is foreign to the person's usual disposition, are serious warning signs. This aggression may at any time be turned by the individual against himself. If the depressed individual goes unexpectedly on a journey, or wanders away with mind clouded (a fugue), he is suicidal.

Feelings of loneliness and of being unwanted are common harbingers of suicidal attempts, particularly in older people.

While none of these several symptoms is found exclusively in the suicidal patient, the presence of any of them will indicate the need for extra caution, and their concentration is always ominous.

Next article on Emergencies in General Practice.—"Obstructed Labour," by Mr. J. Peel.

Refresher Course Books.—Copies of the first two volumes of collected articles from the Refresher Course for General Practitioners published in the *Journal* are still available at 25s. (postage 1s.) each. The first volume contains 55 articles and the second 60. Each article has been revised and brought up to date by its author.

These books may be obtained from the Publishing Manager, B.M.A. House, Tavistock Square, London, W.C.1, or through any bookseller.

MUSIC IN MEDICINE

Galen advised playing music to cure snake bite, Pythagoras thought music good for depression, and more recently a dentist claimed that he needed less gas for his anaesthesia if he played Debussy's "Clair de Lune" or "The Moonlight Sonata" on the gramophone at the same time. These were a few of the examples quoted by Mr. FRANK HOWES, music critic of *The Times*, in the third Cantor Lecture given to the Royal Society of Arts on February 21. Mr. Howes is a member of the council for music in mental hospitals, which for the past ten years has tried to make systematic provision of music for psychiatric in-patients, and has sponsored investigations, particularly by the late Dr. Mitchell at Warlingham Park Hospital, into the therapeutic value of music. In one experiment soothing music was played to disturbed patients at bedtime, instead of giving them sedatives, but the only result was a fight. In another, when the last two movements of Vaughan Williams's F minor symphony were played to a group of neurotic patients, the effect was to bring into the open their hostility to psychiatrists, which was freely expressed.

Dr. Cunningham Dax at Netherne Hospital had played music to patients and then made them paint their response. Their pictures showed either elation (after Mahler's adagietto) or depression—after Mendelssohn's "Midsummer Night's Dream." Thirteen out of seventeen pictures were of violence, robbery, murder, and a Chopin nocturne provoked a suicide. Bach and Mozart were probably tranquillizing. But the hope of a musical pharmacopoeia was dashed by the inconstancy of the effects. Results were so often unexpected, or varied with the individual. With some, music provoked an emotional explosion and release which was beneficial; in a few others, epilepsy; and yet others remained indifferent to it. But there are different types of listener, susceptible of classification like other personality attributes. We all listen in various ways, but predominantly in one way characteristic of us. A simple classification, went on Mr. Howes, was Vernon Lea's, into Sicilians (those susceptible to the sheer power of sound, sensuous euphony), dionysiacs (those who respond to the emotion), and apollonians (the intellectual–technical approach). Only the second group was likely to be therapeutically approachable. Mr. Howes's own estimate of music in hospital was modest and commonsensical. An American authority, Dr. S. Licht, in his *Music in Medicine* (1946) thought the music played should be bad music, an endless succession of old-time favourites, but Mr. Howes believed that in-patients were a cross-section of the public with the same musical tastes, and needed something not too long or complicated, but not too well known either. Music for them could be a part of occupational therapy and an entertainment. It might make some temporarily less introspective, in a few it might awaken a new and lasting interest, but above all it was a communal activity, and brought solitary people into contact with their fellows. Those who played had in addition the satisfaction of exercising a skill and of creating something. Beyond that it was difficult to say. Plato in his *Republic* laid great stress on music as an element of education, because rhythm and euphony entered into the inner recesses of the soul and made a man a well-ordered person—an idea which was very foreign to us to-day. We were more accustomed to the thought that music speeded industrial production, or human performance, and Mr. Howes quoted an odd experiment from 1911, when 46 mile-long bicycle races were ridden, 23 to music and 23 in silence. The average speed of the control group was 17.9 m.p.h., and that of the musically stimulated 19.6. To sum up in a sentence, music is certainly hygienic, even if not therapeutic.

Reports of Societies

DEFECTS IN MODERN TREATMENT OF LEPROSY

The introduction of the sulphones for the treatment of leprosy a few years ago aroused world-wide interest and great hopes for the eventual eradication of the disease. But to-day opinion, if no less hopeful, is certainly becoming more critical. Speaking on March 2 before the Edinburgh Branch of the Royal Society of Tropical Medicine, the director of the newly established East African Leprosy Research Centre, Dr. JAMES ROSS INNES, roundly declared: "The modern treatment of leprosy based on the sulphone group of drugs is unsatisfactory." He realized, he said, that many would think this statement outrageous, when they recalled the few lepers who ever came within sight of cure during the chaulmoogra era; but it was high time leprologists expressed their dissatisfactions as a preparation for further advance.

Limitations of the Sulphones

Broadly speaking, the sulphones brought clinical arrest and bacterial negativity to a high percentage (70 to 80) of active cases of leprosy, the relapse rate was low, and relapses were easily reversed. Dosage was moderate, drug reactions were infrequent, and the annual cost was low. Useful adjuvant drugs were also available, such as isoniazid, thiosemicarbazone, A.C.T.H. and cortisone, streptomycin, chlorpromazine, and vitamin B_{12}. Drug resistance to the sulphones proper was practically unknown. In fact the whole therapeutic picture seemed rosy. "We ought to be able to 'plug away' with the sulphones and clear leprosy from the face of the earth." But, said Dr. Innes, after experience of the sulphones on a large scale it was by no means certain that this would be so.

For one thing, it took far too long to achieve bacterial cure in lepromatous cases. A failure rate with the sulphones of 20 to 25% in various countries indicated their inadequacy. Instead of achieving bacterial negativity in six months to a year, which would be a useful period in controlling the spread of the disease and a fair one to expect, they took three to five years or more. It was true that when widely and carefully applied in an endemic country the sulphones achieved great things, but their slowness and imperfection

of action suggested that it might prove very hard to eradicate the hard core of endemic infection. "Leprosy patients soon discern that the drug has power and wait as patiently as they can for the final happy result, but few escape periods of doubt and despair as month succeeds month. In some of them, hope dies, and this reacts unfavourably on their prospect of ultimate cure." What is wanted, said Dr. Innes, is a dynamic bacteriostatic or bactericidal drug, or combination of drugs, stronger than the sulphones, both for the sake of the leper himself and for the sake of the community.

Other Weaknesses

Quite apart from the sulphones, there were other serious weaknesses in the attack. The criteria of cure were still too vague. Laboratory checks were few and limited. Clinicians could not tell how many resting bacilli, or viable granules or debris of bacilli, might lie low in the tissue planes. In the last resort, if biopsies detected nothing, they had to fall back on long periods of observing their patients. Then, there was no way of modifying the resistance of the patient with leprosy. They badly needed an agent that would stimulate direct resistance to the infection. The lepromin test did not do this; it indicated only the degree of resistance already present. Nor was there any evidence that B.C.G. inoculation raised the resistance of the leper to his disease, although some had suggested that it might be a valuable prophylactic.

Perhaps also, in the understandable enthusiasm for the sulphones, the use of hydnocarpus oil had been abandoned too readily. Local intradermal injections were still useful in resistant tuberculoid and indeterminate lesions. The trouble with hydnocarpus oil was that the dose was large and the injections took such a time.

Tuberculosis and Leprosy

Finally, Dr. Innes indicated the tardy co-operation between tuberculosis and leprosy workers in countries where both diseases were rife. There were many points of similarity between the two diseases. "In leprosy therapy the only sound policy at present is to investigate drugs which have an action in human tuberculosis or on the human tubercle bacillus." Likewise, tuberculosis workers could gain from the trial of drugs in leprosy. Closer co-operation was long overdue, and great benefit to both sides would result from it. In East Africa, for instance, with almost a quarter of a million cases of leprosy and probably an equivalent number of cases of tuberculosis, co-operation should be at all levels—in control, therapy, follow-up, and research.

LOCAL MEDICAL SOCIETIES

Manchester Medical Society

During a discussion on January 24 on "Recent Advances in Obstetrics and Gynaecology," Dr. R. NEWTON, a clinical lecturer in the subject at Manchester University, told the Section of General Practice that he questioned the usefulness of many of the investigations undertaken in cases of infertility. Nevertheless, he went on, there was a useful by-product of these investigations—the discovery of many early cases of tuberculous endometritis and salpingitis. Reports on their treatment with streptomycin and P.A.S. were more hopeful.

Basingstoke Plastic Centre Medical Society

On February 17 the Society held a symposium on "Fractures of the Long Bones with Soft Tissue Loss," the speakers being Professor J. TRUETA, Mr. J. S. ELLIS, Mr. A. J. EVANS, and Mr. E. W. PEET. In the healing of fractures, said Professor Trueta, the periosteal vessels were most important. Stripping of the soft tissues away from the periosteum reduced the blood supply at the fracture site and delayed union. His own work had convinced him of the importance of early skin repair in long-bone fractures. This view was shared by Mr. Ellis, who said that good results had been obtained when simultaneous skin and bone replacement was carried out within a week or two of injury. Mr. Peet discussed the technique of skin repair in these cases, and Mr. Evans reviewed a series of 39 cases treated at Rooksdown House between 1940 and 1945. This series showed a strong preference for the cross-leg flap, and included nine successful examples of simultaneous skin and bone replacement.

Liverpool Medical Institution

"Tin-smelters' pneumoconiosis" was the subject of a paper read to the Institution by Dr. P. H. WHITAKER and Dr. A. JOHN ROBERTSON on February 10. During a field survey 120 cases of pneumoconiosis were found at a tin-smelting works. A film was shown illustrating the main sources of dust formation and the smelting process. Dr. Whitaker then demonstrated some typical chest radiographs from the men and Dr. Robertson presented some preliminary clinical, environmental, and experimental studies in support of the view that the condition is a benign pneumoconiosis due to tin oxide.

Correspondence

Because of the present high cost of producing the Journal, and the great pressure on our space, correspondents are asked to keep their letters short.

Adrenalectomy for Breast Cancer

SIR,—I have read with considerable interest your leading article entitled "Adrenalectomy for Breast Cancer" (*Journal*, January 1, p. 33). I should like to comment on the endocrine types of breast cancer—namely, ovary-dependent, adrenal-dependent, and hormone-independent.

My colleagues and I have discussed this subject previously,[1] classifying breast cancer into two types—namely, oestrogen-dependent and non-oestrogen-dependent. Our studies demonstrated that approximately 50% of pre-menopausal women with metastatic breast cancer have an oestrogen-dependent type of tumour, as shown by the fact that oophorectomy results in cessation of growth and regression of the tumours, subsequent administration of oestrogen to the patient produces reactivation of the tumour growth, and on withdrawal of the oestrogen the tumours again regress. In the other 50% of cases oophorectomy produces no benefit and oestrogen fails to stimulate tumour growth.

We have also presented evidence which suggests that adrenalectomy produces its benefit by removal of another source of oestrogen. Thus pre-menopausal women who have obtained a remission from oophorectomy may obtain a second remission from adrenalectomy; whereas those who fail to benefit from castration invariably fail to benefit from adrenalectomy also. This information provides the only practical means of selecting patients for adrenalectomy. In post-menopausal women combined oophorectomy and adrenalectomy will benefit about 50% of patients and is the treatment of choice, since oophorectomy rarely produces a remission.

The leading article also raised the question as to whether human mammary cancer may be dependent upon pituitary hormones for its growth. We have presented preliminary observations which indicate that some tumours are probably growth-hormone-dependent.[2] Thus, hypophysectomy has produced remissions in patients whose disease had relapsed after oophorectomy and adrenalectomy. In one of these patients administration of a beef pituitary growth hormone preparation caused acceleration of the tumour growth, which subsided when the growth hormone was withdrawn.

Hypophysectomy for the treatment of metastatic mammary cancer in man is being pursued with the hope

of attaining a higher percentage of response and longer-lasting remissions.[3] It is already apparent, however, that in some patients the disease is unaltered by ablation of all three endocrine organs.—I am, etc.,

New York. O. H. PEARSON.

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Advertising by Post

SIR,—The bombardment of advertising material aimed at general practitioners by every morning's post has recently increased to a full-scale barrage. If anyone were seriously to attempt to read all this verbiage, it might take two or three hours every day to get through it, but in practice 90% of it goes unopened into the waste-paper basket. Ultimately the public has to pay for this appalling waste, and in the interests of manufacturing firms and doctors alike it seems to me very desirable to try and do something about this. However, most doctors find it necessary to use a certain number of proprietary preparations, and information about new products is necessary and often very interesting and instructive.

I have suggested to representatives of many different firms that a card should be prepared for every product with certain necessary information only recorded on it such as indications, composition, dosage, contraindications, and price, and that the size of these cards should be standardized by all firms so that they can be easily filed for reference in a simple box. At present the number of pamphlets is so excessive, and they are so different in shape and size, that filing is impracticable. This suggestion has been well received by most representatives, although many expressed the view that it was too much to expect that all firms would agree on this. But the advantages of such a scheme would seem to be so great that in my opinion it would be well worth while for the manufacturing firms to consider it. And if only a few firms started with my suggestion, the rest might soon find it advisable to follow suit.

If in addition the manufacturing firms could come to some agreement between themselves to limit the advertising pamphlets about any particular product to a certain number per year, I believe that this would also be of great benefit to all concerned, and some doctors might even read them.—I am, etc.,

Sandwich, Kent. A. K. JONES.

Trichomonal Vaginitis

SIR,—I have been very much interested in the correspondence opened by Mr. Aleck Bourne (*Journal*, January 22, p. 226) on the problem of the resistant and relapsing case of trichomonal vaginitis. Mr. Bourne emphasized that the trichomonas may be found as an inhabitant of the healthy vagina and may be almost entirely absent in a clinically severe case of recurrence of the disease, yet other correspondents have said little about these underlying causes and predisposing factors which surely are the most important aspect of the problem.

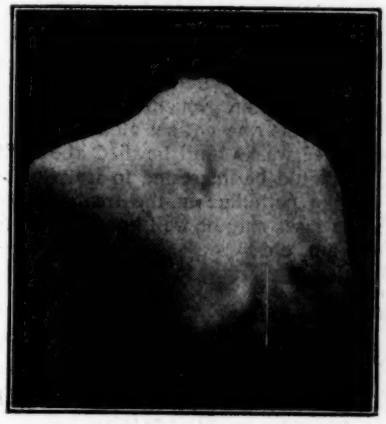
I suggest that in addition to the frequent association of secondary bacterial infections and monilia (and possibly virus infections), which require their own appropriate treatment before the condition can be cleared, and the by no means rare allergic manifestations in sensitive individuals, one or more of the following factors may play a part: (1) An endocrine factor—indicated by the tendency to relapse in the post-menstrual phase. At this time cyclical ovarian activity is at its lowest ebb, the vaginal epithelium is inactive, leucocytes are few, and the secretion less acid, and the trichomonas is encouraged (it is my clinical impression that the woman with highly active ovarian function rarely suffers from vaginitis). (2) A neuromuscular factor: a woman with an irritating vaginal discharge tends to hold the vaginal introitus closed, which may become so much of a habit that a state of vaginal spasm is induced, and this may well retard recovery by retaining secretion and squeezing organisms into the many available hiding-places. (3) A urinary factor: a gaping introitus and lax vaginal wall lead to constant soiling with drops of urine after micturition, and this admixture, if highly acid or alkaline, may so alter the *p*H of the vaginal secretion that conditions are favourable for the trichomonas to flourish. The importance of the urinary factor is seen in the vulvo-vaginitis of diabetics, which, although admittedly more often due to a monilia and secondary bacterial infection than to trichomonal vaginitis, may resist all treatment until the urine is kept more strictly sugar-free—or is it that the lowered blood sugar affects the glycogen content of the vaginal mucosa? (4) Certain contraceptives: women who have had an attack of trichomonal vaginitis are not able to use with impunity some of the contraceptives which are entirely innocuous to others.

Knowledge of the means of increasing the powers of resistance of the vaginal mucosa to the trichomonas seems a more effective method of attack than either the production of stronger or the use of larger dosage of anti-trichomonal drugs.—I am, etc.,

Hove, 3. MARGARET NEAL-EDWARDS.

Subscapular Swellings

SIR,—On January 4, 1955, a young housewife presented with bilateral subscapular swellings. These had been insidious in onset and quite painless. The patient's attention was drawn to them by her husband, who remarked that she was becoming round shouldered. She had been doing extra housework of recent weeks, but had also acquired a rather boisterous dog that she exercised daily on a lead. The patient had had a chronic cough over the past two to three years.



Four and a half ounces (128 ml.) of heavily blood-stained fluid was withdrawn from the right side at the first attendance and 3¼ oz. (92 ml.) on January 31. A proof puncture only was made on the left side, where the quantity of fluid has gradually increased over the past four weeks. It has been suggested that (1) there was bilateral tearing of rhomboid major, (2) tearing of latissimus dorsi, (3) friction between subscapularis on the deep aspect of the scapulae, the serratus anterior, and the chest wall, and (4) that it is an inflammation of unusual bursae.

I should like to thank Professor Lockhart and Dr. Fyfe, of Aberdeen University anatomy department, for their interest, and Mr. Wilsher, of Chesterfield, for the photography.—I am, etc.,

Chesterfield. KENNETH E. MCIVER.

Cancer and Tobacco

SIR,—I enjoyed your leading article entitled "Carcinogens in Cigarettes" (*Journal*, November 20, 1954, p. 1213), but wish to suggest that perhaps there has been too much emphasis upon the need for combustion to produce carcinogenic agents from cigarettes. There is good clinical evidence from India, Ceylon, the United States, and other countries that the habitual use of chewing tobacco alone or with additives is associated with the development of tumours at the "quid-site."

The apparent association of cancer and the use of tobacco, whether burned, unburned, and with or without additives,

paper, insecticides, etc., would suggest that the carcinogenic property is an inherent one. If lung cancer is caused by heavy cigarette-smoking, it is probably the result of a quantitatively higher exposure of a susceptible tissue by the carcinogenic agent; one would expect the larynx also to have a higher incidence of tumours. Tobacco chewers, in contrast, should be expected to have a high incidence of oral cancers, hypopharynx, and oesophagus. Pipe and cigar smokers apparently swallow more tobacco products than they inhale, and therefore would be expected to fall into this group.—I am, etc.,

Buffalo, 3, N.Y. GEORGE E. MOORE.

Cardiac Asthma

SIR,—I read with great interest Dr. J. G. M. Hamilton's article on "Cardiac Asthma" in the "Emergencies in General Practice" series (*Journal*, January 1, p. 39), and would like to make one addition to his suggestions for immediate treatment. Instead of morphine, I now use only pethidine—usually intramuscularly but if necessary intravenously—or sometimes half dose by one route and half by the other. The dose is normally 100 mg., and the results are as dramatic as one would wish, no oxygen or any other medicament—e.g., aminophylline intravenously—being required in the majority of instances.

I was introduced to this drug as a cure for asthma by Dr. A. H. Walker, the house-physician at the Lowestoft and North Suffolk Hospital, in 1952, when I sent in a small girl of 6 years with a severe attack of "adrenaline-fast" bronchial asthma, and he injected pethidine, 50 mg. (I think that was the dose), and cured the attack in 20 minutes. Following this example I have used it in a few cases of bronchial asthma where adrenaline has failed, and in all cases of cardiac asthma, which have been fairly numerous in my practice, as one patient alone suffered one attack every two or three weeks until he died about 12 months ago.

I should be interested to learn of other observations concerning pethidine in the treatment of asthma. Its use in these cases may be well known, but my belief is that it is not.—I am, etc.,

Lowestoft. T. S. NICOL.

Changes in the Mental Health Services

SIR,—I would like to make a comment on your recent correspondence over the importance of observation wards in the mental health service.

In regard to the observation ward, I too, like one of your correspondents, Dr. I. S. Kreeger (*Journal*, January 8, p. 104), have spent a similar period in the same observation ward (that now attached to a teaching hospital) and also a period in another observation ward, between them dealing with a very large proportion of London's mentally sick. It seems to me that all three correspondents are right: Sir David Henderson (p. 104) in pointing out the Scottish method of dealing with those problems by admitting them directly to general hospital; Dr. J. B. S. Lewis (*Journal*, December 4, 1954, p. 1354) by suggesting that observation wards should be abolished; and Dr. Kreeger by pointing out how valuable and important the work of observation wards is. A recent article in the *Lancet* by Dr. J. F. Stokes *et al.*[1] has shown, on figures from the same observation ward as Dr. Kreeger and myself have worked in, the very high proportion of physically sick patients admitted to the observation ward with apparent mental disorder.

All these distinguished contributions surely point to the abolition of the observation ward as such, as Dr. Lewis suggests, and to the establishment of properly equipped psychiatric wards within the general, and particularly the teaching, hospital—as Sir David Henderson points out is now the method in Scotland. This would mean that, as Dr. Kreeger rightly asserts, the valuable and important work now done in observation wards will be carried on side by side with other medical and surgical specialties and given its rightful due—of which it is still deprived by many within the medical profession. It would mean that social, psychiatric, medical, and medico-legal problems at present kept inside the observation wards would be properly ventilated, explored, and, very much more important, taught to students, instead of being relegated to a minor, unimportant role in a full curriculum; and taught with appropriate case material at the bedside in the most reputable clinical fashion. It would help to underline the complex interrelation between the psyche and the soma in all disease, whether mental or physical. It would also mean that the nursing of such cases could be shared by nurses fully trained in both aspects of nursing and teaching programmes integrated to this end. It might also help the enormous difficulties of attracting suitable men and women into the nursing of the mentally disturbed, instead of maintaining an increasingly unreal isolation. Within this framework more cases could be dealt with by treatment on the spot, later discharge, out-patient support, and follow-up than is now possible. The burden could be more effectively lightened on the mental hospitals, as well as establishing closer relation between the mental hospitals and the general hospitals, and the difficulties surrounding certification and mental disease more easily circumvented in the lay mind.—I am, etc.,

London, N.W.1. M. J. ROSENTHALL.

REFERENCE

[1] *Lancet*, 1954, 2, 862.

Grants for New Hospitals

SIR,—Your leading article "Grants for New Hospitals" (*Journal*, February 15, p. 466) is timely in two respects; first, in stating that the reason for priority of some projects is not clear, and, secondly, in indicating the possible danger of attracting staff away from old hospitals to new ones.

The situation in the North-west Metropolitan Region is of some interest. Certain of the urban hospitals are unable to meet their commitments fully or efficiently. It is however stated that there is no question of adding to their beds while beds stand empty elsewhere. The hospitals in question are, however, struggling to deal with their work under most difficult conditions. Additional accommodation in such hospitals would cost but a fraction of the capital outlay on some of the proposed new hospitals. A hospital of 150 beds is planned for the Welwyn Garden City and Hatfield area (an ultimate bed total of more than 400 was mentioned by an official of the Regional Board in a press interview). At the present time the hospital work of the Welwyn Garden City and Hatfield area goes mainly to St. Albans, Hertford, and Barnet. The hospital at St. Albans consists of three separate units, with inadequate *x*-ray and theatre facilities, as well as many other difficulties. Despite these handicaps, this hospital and others drawing patients from the Welwyn Garden City and Hatfield area still have unused reserves. What justification can there be for planning a further hospital which may exceed in size any of those already draining this area? Much of the increase in population has already occurred, and even at its peak will result in about a 25% increase of the total population. To say this is not to deny the need for improved hospital facilities in the area concerned, but merely to question the scope and detail of the present plans.

You, Sir, press for the publication of reasons for various decisions, and I am sure this will receive wide support. One might also put in a plea for prior consultation with those who provide the service. So far as I am aware, the medical advisory committee of the group to which I have referred (representing hospital staff, general practitioners, and medical officers of health of the area) have not been consulted about details of the proposed Welwyn Garden City and Hatfield Hospital. It is hard to see how the Ministry can get a true idea of the medical requirements of such an area without consulting the professional people on the spot.

If I have referred to one particular area, it is only because of my personal knowledge of it. I have, however, no wish to imply that the conditions there are necessarily any less satisfactory than elsewhere, nor do I wish to attribute

responsibility for that state of affairs. Speaking as a doctor and a taxpayer, I am by no means satisfied that the best, or even the second best, will be done with the available resources.—I am, etc.,

Radlett, Herts. R. S. MURLEY.

Alcohol as a Diuretic

SIR,—Dr. Lawrence Mackie's copy of *Macbeth* "shows Act II to have but two scenes" (*Journal*, February 12, p. 415), and he implies that Professor L. J. Witts must have given the wrong reference when he wrote of the dialogue between Macduff and the porter (*Journal*, January 29, p. 271). In the First Folio (1623) Act II consisted of *four* scenes. It was Nicholas Rowe (1709) who reduced this Act to two scenes. Evidently Dr. Mackie's *Macbeth* follows Rowe's arrangement. A modern example of this is the Shakespeare published by Collins about 30 years ago: the name of the editor is unknown, but the book can be identified from the fact that it includes an exhilarating introduction from the pen of St. John Ervine dated June, 1923. Happily, Collins's new edition, prepared by the eminent Shakespearian scholar Peter Alexander, reverts to the arrangement given in the First Folio.

"What, I wonder, did the porter at Inverness castle drink?" asks Dr. Mackie. I gather that he is not offering a prize for the correct answer. As a former citizen of Inverness, I feel entitled to suggest that "carousing until the second cock" means only one thing, no matter whether we consider it by the standards of the twentieth century or by those of King Duncan's time. Revelry amounting to "carousing" was almost certainly sustained by liberal indulgence in an alcoholic beverage of some kind. It is probable that the porter had been drinking whisky or other spirituous liquor. "Distilling was practised in England as early as the eleventh century, but was confined to the monasteries, the produce being used as a medicine. . . . In Scotland during the fourteenth century whisky had already displaced much of the imported Continental spirit. . . . By the middle of the sixteenth century a large trade was established, and house or cottage stills were found in all parts" (*Chambers's Encyclopaedia*, 1904). It is unnecessary for Dr. Mackie to insist that the porter "be shown to have ingested pure alcohol." No self-respecting Scotsman would thus abuse his stomach; nor would he waste "pure alcohol"—a preparation rarely seen, even in the laboratory of the analytical chemist. The product of the pot-still distillery contains 80% of pure alcohol when 50% over proof; the patent-still yields a spirit containing about 95% alcohol.

It has long been held that the presence of alcohol in the blood produces diuresis independently of the water and ethereal substances which are imbibed with most alcoholic beverages. As a therapeutic measure, the action is perhaps unimportant; and in any case alcoholic beverages would rank among the most expensive preparations for producing a flow of urine. On the other hand, if it does occur, the diuretic action of alcohol must be a matter of some interest to physiologists and pharmacologists. We may be sure that academic niceties about higher esters and the like had no place in the mind of the porter at Inverness castle. He had evidently been impressed by what might be called the over-all effects of alcoholic beverages taken late at night; perhaps he had evolved a crude test of diuretic potency by simply noting the number of times he had to rise during the night to empty his bladder.

Dr. Mackie is evidently not convinced that excessive drinking causes a red nose. Whatever may be the importance of alcohol in the pathogenesis of redness of the nose, it is certain that this disfigurement is by no means rare among those of temperate habits, and florid cases have been observed even among strict abstainers. Nevertheless, a flushed face is one of the early signs of an alcoholic orgy, and over a period of years the face of the inveterate drinker often becomes both congested and coarse. I do not suggest that the action of alcohol is selective in the sense that the skin of the nose is particularly liable to be affected, but in the presence of other diseases such as acne rosacea alcohol may intensify redness of the nose to an alarming degree. It is probable that Bardolph was a victim of this distressing combination of disabilities—rosacea and alcoholism. When Fluellen was describing him to King Henry V he said: ". . . his face is all bubuckles, and whelks, and nobs, and flames o' fire; and his lips blows at his nose, and it is like a coal of fire, sometimes plue and sometimes red; but his nose is executed and his fire's out" (*Henry V*, Act 3, Scene 6, line 101). The aetiology of this condition is suggested by a conversation that takes place before the Boar's Head tavern (Act 2, Scene 3, line 40) *à propos* some of the foibles of the late Sir John Falstaff.

Boy.—Do you not remember 'a saw a flea stick upon Bardolph's nose, and 'a said it was a black soul burning in hell?

Bardolph.—Well, the fuel is gone that maintained that fire: that's all the riches I got in his service.

Doubtless the fuel was sherris-sack—so eloquently eulogized by Falstaff in his soliloquy on wine (*Henry IV*, Part II, Act 4, Scene 3):

> . . . A good sherris-sack hath a twofold operation in it. It ascends me into the brain; dries me there all the foolish and dull and crudy vapours which environ it. . . . The second property of your excellent sherris is the warming of the blood. . . . It illumineth the face, which as a beacon, gives warning to all the rest of this little kingdom, man, to arm. . . .

—I am, etc.,

Glasgow, W.2. STANLEY ALSTEAD.

Prevalence of Dysentery

SIR,—It is satisfactory to see that you gave your leading article (*Journal*, February 12, p. 401) to this important disease, but I think you are mistaken in attributing its lessened severity amongst the young and healthy to the higher proportions of Sonne as opposed to Flexner infections. Experience over the last dozen years is that both types of dysentery have been much milder, and the diarrhoea has been as a rule of moderate intensity, with blood and mucus, prostration, and high temperature only exceptionally. The reason for this change is unknown, but perhaps the constitution of the organisms has been altered and virulence diminished as a result of widespread sulphonamide therapy.

This decrease in virulence, however, carries a new danger, for it has led the public to treat the disease with complacency. Bacteriological tests of the stools are often omitted, so that carriers abound, and, as your leader showed, the disease is assuming serious endemic proportions. Complacency is unjustified, since, although the mortality amongst healthy adults may be trivial, it is not so in the invalid aged; moreover, the disease is still severe and frequently fatal in infants.—I am, etc.,

Warwick. E. S. STERN.

Chlorpromazine

SIR,—In your leading article on chlorpromazine (*Journal*, February 5, p. 338) you state that the main control of body temperature is due to tonic impulses passing down the voluntary nerves to skeletal muscles, and later you ascribe the hypothermic properties of chlorpromazine to a peripheral neuromuscular depression. Recent work has suggested that under normal conditions skeletal muscle activity plays a negligible part in the maintenance of body temperature, the main centres of heat production being the liver and the brain.[1,2] The shivering mechanism comes into operation when active cooling of the body is carried to such a degree that the normal heat conservation mechanisms can no longer maintain body temperature. Neuromuscular blocking agents may be used as adjuvants in the production of hypothermia by surface cooling, when they prevent reactive shivering, but are useless as the primary agents to induce hypothermia.

If chlorpromazine produced hypothermia by neuromuscular block one might expect even the surface of the

limbs to be cooler than the rest of the body, whereas the mild fall in body temperature induced by clinical doses of chlorpromazine is characterized by the warm state of the extremities.[3] It would appear likely that in the hypothermia induced by chlorpromazine a defect in heat conservation is more important than any derangement of heat production.—I am, etc.,

London, W.C.2. C. M. CONWAY.

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2 Birnie, J. H., and Grayson, J., *J. Physiol.*, 1952, 116, 189.
3 Dobkin, A. B., *et al.*, *Anaesthesia*, 1954, 9, 157.

Hair-grips as Foreign Bodies

SIR,—Mr. Ralph H. Gardiner's memorandum (*Journal*, February 12, p. 397) serves a very useful purpose in drawing attention to the special dangers of the swallowed hair-grip. It requires operative removal much more commonly than any other swallowed foreign body. I feel that Mr. Gardiner was too impatient when he operated on his patients after the hair-grips had been in the stomach for only 5 and 10 days. Foreign bodies don't usually do any harm there, and I have seen hair-grips pass the pylorus and manipulate the alimentary canal successfully after lying in the stomach for three weeks.

When a grip gets arrested in the bend of the duodenum it may erode the bowel wall, and operation is indicated. The sequelae to erosion, however, are not as dramatic as might be inferred from Mr. Gardiner's article. Of the four grips which I have removed and which were lying partially or completely outside the bowel wall, none had caused more than localized peritonitis and the clinical features were mild abdominal pain and local tenderness. One hair-grip was removed from a deep abscess in the abdominal wall. No faecal fistula developed.

I cannot agree with his treatment of bulky diet and "normacol." The most important objective of treatment is to prevent intestinal spasm. This is best achieved by giving the child the diet it is used to. For this reason it would seem wise not to admit these children to hospital, once it is ascertained that the object has entered the stomach, but to supervise them carefully as out-patients.—I am, etc.,

Manchester, 3. H. M. GOLDBERG.

Agranulocytosis

SIR,—Drs. D. G. Wraith and F. Dudley Hart in their letter (*Journal*, February 12, p. 412) advocate the use of cortisone and A.C.T.H. in the treatment of drug-induced agranulocytosis, and cite a number of cases which recovered following the exhibition of these drugs. Cases have also been described by Kirkeby[1] and Peyman[2] which responded to A.C.T.H. and cortisone, although the latter considered the marrow was probably recovering before the drug was given.

There have, however, been a number of cases recently[3–9] which recovered on antibiotics alone without the use of A.C.T.H. and cortisone, and one[10] who probably would have recovered, as well as some cases[11–13] who did not respond or died after the use of these drugs. In an annotation[14] you say: "In agranulocytosis the drugs [that is, A.C.T.H. and cortisone] have given far less benefit, a favourable response being a rare and unpredicted event." The use of these drugs is also not without risk especially in the presence of an established infection—a common enough event in agranulocytosis. In a further annotation[15] you state: "It is now fairly well established that all the common bacterial infections are enhanced [by the use of these drugs], including those with spirochaetes and tubercle bacillus"; and Page[16] states: "Little emphasis has been laid on the practical results of the well-known disseminating qualities of these drugs in occult infections.

Two cases of drug-induced agranulocytosis have been treated in this hospital in the past eighteen months. One was a woman who had had sulphonamides, chloramphenicol, and a compound of amidopyrine and a barbiturate, and who had on admission a white cell count of 600 per cubic mm., with no polymorphs present. She was treated by antibiotics initially, but A.C.T.H. was started on the fourth day. No polymorphs appeared in the peripheral blood until a few hours before her death on the tenth day. The second case was a woman who had had phenobarbitone for six weeks, and was admitted because she had a generalized maculopapular rash and sore throat. Her white cell count was 170 per cubic mm. with no polymorphs. She was given penicillin, and on the fourth day after admission her temperature settled and polymorphs reappeared in the peripheral blood. She is now quite normal.

Hutt and Lee[17] suggest not giving A.C.T.H. and cortisone for at least seven days, because the marrow frequently recovers in this time. It is possible that our first case would have recovered without the use of A.C.T.H. and that she died of a septicaemia induced by this drug. Post-mortem examination confirmed that death was due to a generalized infection, with meningitis and bronchopneumonia.

There is therefore need for considerable caution in the use of A.C.T.H. or cortisone in treating agranulocytosis: and it would seem desirable that a properly controlled trial of these drugs in agranulocytosis should be made. The Medical Research Council trials have so far been quite inadequate, as in the first report[18] no case of agranulocytosis was included and in the second[12] only two. Aber and others[13] quote only three cases in their report, and Whitby and Britton[19] quote only Hart's case.[20] We also do not know how many cases have been treated unsuccessfully by A.C.T.H. and not reported. I suggest that the case for A.C.T.H. or cortisone in drug-induced agranulocytosis is not proven.

I am grateful to Dr. R. G. M. Longridge for permission to include the clinical notes of these patients.—I am, etc.,

Salisbury. J. R. H. PINKERTON.

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14 Ibid., 1954, 1, 32.
15 Ibid., 1954, 1, 381.
16 Ibid., 1954, 2, 1334.
17 Ibid., 1953, 1, 784.
18 Ibid., 1952, 1, 1261.
19 *Disorders of the Blood*, 1953, 7th ed. London.
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Silver Stool Sign

SIR,—Mr. Arnold S. Aldis in the interesting case he reported exhibiting silver stool (*Journal*, February 12, p. 414) suggests it would be interesting to hear if others had observed this phenomenon.

In south China and Hong Kong I have on several occasions observed silver stools in patients suffering from tropical sprue. All were advanced cases of this disease and all were undergoing treatment with large doses of calcium lactate by mouth and twice-daily doses of parathyroid gland, gr. 1/10 (6.5 mg.), as this was said to regulate the amount of calcium absorbed into the system. Sprue cases do not exhibit blood in the stools, unless there is some superimposed cause to account for the blood, but of course there is little or no bile and usually an excess of fat in sprue stools.

It was suggested that the action of the fat on the calcium, aided by the parathyroid gland, and with no bile pigment to obscure the reaction, gave rise to the silver stool, so aptly described by Mr. Aldis as just like aluminium paint. In these sprue cases there was no question of cancer of the ampulla of Vater or cancer at any other site, but silver stool was regarded as a serious and often fatal complication in tropical sprue.—I am, etc.,

Belfast. J. H. MONTGOMERY.

The New Insulins

SIR,—Dr. E. B. Kraus writes (*Journal*, February 19, p. 478) about the virtues of isophane insulin (N.P.H.), produced originally by Hagedorn in Denmark and widely used in the U.S.A. since 1948. He says that it has received little publicity in Britain; but that does not mean that it has not been studied by some of us on our own patients and its effects observed on travelling Americans. My opinion was, and is, that, containing very little protamine, its action as a one-dose preparation is not much more prolonged than globin insulin. It works well, as do other slightly retarded insulins, on the milder insulin case but will not carry through for 24 hours in the average severe case needing some 40 to 60 units a day. It is therefore not lack of trial and knowledge that has led to silence in the British medical press.—I am, etc.,

London, W.1. R. D. LAWRENCE.

Princess Louise Children's Hospital

SIR,—Dr. R. W. Smithells (*Journal*, February 19, p. 479) recalls the "Battle of Paddington Green" in writing of the threat to convert the Princess Louise Hospital for Children to adult use. It was in 1949 that the Sporborg Subcommittee recommended the Board of Governors of St. Mary's Hospital to close Paddington Green Hospital as a children's unit. And it was outraged public opinion, which was prepared to chain itself, its prams, and its babies to the railings of St. Mary's, which finally made the board abandon the proposal.

In their latest report the Sporborg Subcommittee say: "Members of the Board may well be surprised that whilst in their earlier proposals . . . the Subcommittee recommended the conversion of Paddington Green Hospital to adult use, they now put forward a similar recommendation in respect of Princess Louise Hospital." And well they may be surprised. For the same arguments against such a conversion apply now as then, and the same solution exists—namely, that if St. Mary's do not need so many cots for teaching paediatrics to their students they should allow one of their two children's hospitals to be transferred to a less favourably placed teaching hospital.—I am, etc.,

London, W.1. MICHAEL HARMER.

Tonsillectomy

SIR,—I congratulate Mr. E. H. Miles Foxen on his protest (*Journal*, February 12, p. 413) against the extraordinary inefficiency of the present removal of tonsils and adenoids in this country as a whole. The rate of failure appears to be about 20%; and the amount of damage to patients and discredit to the profession caused by this misuse of an excellent operation is immense. He is right in emphasizing that the true principles of tonsillectomy were laid down by George Waugh,[1] since in many clinics the term "dissection" is applied to the use of a snare, after a preliminary loosening of the upper pole.

May I suggest that, in addition to applying to this operation the standards of surgery aimed at in other branches, we might also teach the true anatomy of the region concerned? Some twenty-odd years ago I put forward my views on this.[2] If I am wrong, they should be controverted: if I am right, a considerable number of children have quite unnecessarily bled to death in the interval from the paratonsillar vein. I may say that no surgeon or anatomist would discuss these views for many years, with the exception of George Waugh himself, who came to agree with me completely.

Some of the points I made are now getting into the anatomy books, but no anatomist has dared to recite the old description of the six arteries of supply and the venous plexus and then announce, "*Nous avons changé tout cela.*" The change is being made gradually, so as not to arouse the dawn of doubt among those who have been taught to recite the anatomy of the books as unquestionable dogma. Of course, the trouble is that anatomists do not get specimens of the developing human body to study and demonstrate; can anyone refer me to a really good preparation showing the adenoids or the tonsils *in situ*? Such specimens of the adenoids would demonstrate that the most popular sizes of curettes are too wide to be used on many children without scarring up the openings of the Eustachian tubes, with results only too familiar to those interested in hearing.—I am, etc.,

London, W.1. DENIS BROWNE.

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2 *J. Anat.*, 1928, **63**, 82.

SIR,—The expression of any views on tonsillectomy is always followed by considerable controversy. This fact alone would suggest that consistently good results are not being achieved in all centres. Mr. E. H. Miles Foxen (*Journal*, February 12, p. 413) has no doubt started a prolonged controversy on guillotine tonsillectomy by quoting and supporting George Waugh's[1] statement that "the cause of failure lies not with the operator but with the type of operation."

May I suggest that the key to it all is anaesthesia? If an inexperienced surgeon is only allowed two minutes' operating time, during some of which time the patient is probably moving, he should be forgiven if the uvula or anything else is extracted rather than the tonsil. But if, on the other hand, as in most other surgical operations, he is allowed good operative conditions without a time limit he can remove the tonsil carefully with a guillotine and then examine the surgical field. Should there be a remnant, and this can happen to the most experienced guillotinist, it can be dissected then and there so that complete removal can be ensured in every case. This technique would appear to combine all the advantages of the old method with all the advantages of the new one. If the cases can be successfully treated at a rate of ten or more per hour I can see no reason to reduce the rate to four or less per hour. The end-result should be the same in either case.

One anaesthetic technique which allows this is $N_2O \rightarrow O_2 \rightarrow$ ether—relaxant if required—with intubation orally or nasally according to the surgeon's wishes. After a gag has been inserted the ether should be turned off and only N_2O and O_2 given. This ensures that the patient will be in a light plane of anaesthesia at the end of the operation regardless of time. Another technique which has been used successfully in Portsmouth on many cases has been designed for an experienced guillotinist. A single injection of thiopentone is given in the anaesthetic room; nothing else is given afterwards. This allows some two to three minutes for surgery and examination. Should tags remain the child is given a relaxant and intubated. This technique is not suitable for a slow surgeon or for one who often leaves remnants.

May I, as one who has seen much harm result from the guillotine, suggest that, properly used, it can still play a major role in good modern surgery. While anaesthetists can provide the operative conditions, this is of no avail should we have a generation of surgeons who have never seen it used and are quite determined that they never shall.—I am, etc.,

Southsea. H. B. C. SANDIFORD.

REFERENCE

1 *Lancet*, 1909, **1**, 1314.

SIR,—Mr. E. H. Miles Foxen (*Journal*, February 12, p. 413) must not be disappointed in his expectation of opposition to his wish to relegate the guillotine operation to the historical section of every textbook. Alas, this wish will never be granted by calling what is indeed the truth a dangerous platitude. The guillotine operation, carried out properly, is a sound procedure.

Trained in a Scottish medical school I saw many cases post-operatively whose tonsils had been removed by the

guillotine method. Later, while a registrar in the ear, nose, and throat department of a London hospital, I saw many cases post-operatively whose tonsils had been removed by the dissection method. I can assure Mr. Miles Foxen that it is not just the guillotine method which is responsible for tonsillar remnants and damage to the faucial pillars, soft palate, etc.

Obviously, with either the guillotine or dissection method, there will be initial failures in the training period of any surgeon. If the failures proceed, then either the operator has not been taught correctly or is inept. To reverse Mr. Miles Foxen's quotation, surely "the cause of failure lies not with the operation, but with the type of operator."—I am, etc.,

Carlisle. J. C. CAMPBELL.

A Case of Phaeochromocytoma

SIR,—In reply to Dr. A. C. Kendall's letter (*Journal*, February 19, p. 482), I would like to state that the perirenal insufflation (*Journal*, February 5, p. 331) was undertaken by the presacral route as described by Blackwood.[1] I have no personal experience of undertaking this procedure by any other route, and I would agree that the presacral route should be used for preference. It would appear that Dr. Kendall has been more fortunate than myself in the results that he has obtained.—I am, etc.,

Liverpool, 1. R. A. C. OWEN.

REFERENCE

[1] *Brit. J. Surg.*, 1951, **39**, 111.

Natural Childbirth

SIR,—Dr. Constance Lang Beynon (*Journal*, February 19, p. 475) entertains a series of fears about natural childbirth and expresses an urgent desire to "ventilate some of the problems before it is too late." With all due respect to an inquiring mind, her letter persuades me that she has neither read, practised, nor closely observed the subject of her anxieties. It may be that, like many of our senior colleagues, she is more occupied with obstetric abnormalities and gynaecological cases. One cannot help feeling she has not often attended natural births, for had she done so it is unlikely she would have expressed fears lest all women might be given an opportunity of similar experience.

This obstetric programme provides the most humane consideration and treatment of mothers and their babies. All of us know that the care of women and the conduct of labour, particularly in many hospitals, leaves much to be desired. This problem must be faced frankly so that we can concentrate on making childbirth a healthier and happier event. Surely we owe this to those who place their confidence in us. It cannot be overlooked that the rapid spread of this teaching across the civilized world has been due, almost entirely, to the women themselves. Had there been no justification for their enthusiasm, it would have died out long ago. If responsible medical men, who conscientiously studied and employed its procedures, had proved it to be harmful it could not have survived their denunciation.

Innovations which imply change of orthodoxy usually meet with professional prejudice or apathy, and this case has not been an exception. In spite of all, natural childbirth has survived 30 years of careful thought, discussion, and trial, and the demand for it steadily increases. Men cannot have babies, but there is no shame in sacrificing their academic "stance and circumpomp" in the cause of kindly and compassionate unselfishness for women who bear babies. Dr. Beynon must not be afraid lest mothers receive a service that can do no harm, but will bring to the majority of them happiness, health, and a fund of family affection.

I agree with Dr. Beynon that "more general and open discussion might be wise at this juncture," but I go further. The time is ripe for a full inquiry into the care of pregnant and parturient women, which should be made by medical and lay investigators who are competent and unbiased. I urged those responsible for our obstetric standards to do this eight years ago. The suggestion had interesting repercussions, but there was no inquiry. Childbirth is a much wider subject than obstetrics, for true motherhood is the cornerstone of domestic and social stability.—I am, etc.,

Petersfield, Hants. GRANTLY DICK READ.

Comparison of Vole and B.C.G. Vaccination

SIR,—As there has been considerable publicity in the daily press following the publication of our paper (*Journal*, January 15, p. 133) one or two explanations are called for.

B.C.G. and vole vaccination of the children in the orphan homes and those of our staff was introduced as a protective measure. Eleven cases of tuberculosis had been notified in the 10 years previous to vaccination, and these did not include any case occurring after the children had left the homes, and there has been a number of such tragic sufferers. No case has occurred since this vaccination was undertaken 3½ years ago. In our report we reviewed the state at the end of two years, and since then many of the arms showing a persistent lupoid reaction have responded well to treatment; the two most severe are now healed. In no case has any child complained of pain or discomfort, and there was no systemic upset. The general health of the children has never been better. The opportunity was taken to compare two tried and established forms of vaccination. The persistent vole reactions were unexpected and it was our duty to record this. Nevertheless, we still consider vole vaccination to have certain advantages over B.C.G.

For the most part the article was fairly and accurately reported, but it is most regrettable that a section of the Press has misrepresented facts which may cause public opinion to be unfairly influenced against a voluntary institution whose first concern has always been the health and welfare of the children. The way in which this publicity has been used brings much discredit to those responsible. They have done a great disservice to the children and those sincerely interested in their problems who give such devoted care as house mothers and fathers. It must be made quite clear that the management acted on medical advice in the best interest of the children. There was a similar outburst when diphtheria immunization was first introduced. Finally, any measure which may prove of help in the eradication of tuberculosis should surely be welcomed.—We are, etc.,

HUGH W. O. FREW.
J. ROMANES DAVIDSON.
Paisley. J. T. W. REID.

Fluoridation of Public Water Supplies

SIR,—To fluoridate or not—that is the question. The Commission on Chronic Illness, an independent national agency founded jointly by the American Hospital Association, the American Medical Association, the American Public Health Association, and the American Public Welfare Association, considered all the available evidence regarding the "effects of fluoridation of community water supplies upon the aged and the chronically ill" in the U.S.A. (report dated Chicago, Illinois, March 17, 1954). In this report the concluding paragraph reads: "The fluoridation of water supplies involves no new experience in human welfare. Over 3,000,000 people are living in ordinary good health on water naturally containing fluorides in the amounts recommended for caries control, *or more*" (my italics). The Commission goes further, urging "American communities to adopt this public health measure as a positive step in the prevention of the chronic disease, dental caries."

As regards the undoubted beneficial effects in so far as the children are concerned, all the evidence points to the difference between caries resistance of children drinking controlled fluoridated waters, which has become "most marked,"[1] as compared with children drinking non-fluoridated waters.

It is indeed curious to read the beginning controversy in the British medical press timed as it is a year or so after a similar controversy here—a controversy that still continues but with abating force, in spite of all the vituperation of the antagonists of the measure, in Massachusetts as elsewhere in the country. Incidentally, there are several anti-fluoridation bills before the present session of the Massachusetts Legislature—the sponsors either very long-haired persons, or very short-haired persons, both groups with their own particular varieties of bias. Very few average individuals, whether they be "men in the street," or "professionals," dental or medical, belong to this extremely vociferous group of anti-fluoridators.—I am, etc.,

Ayer, Massachusetts. K. I. E. MACLEOD.

REFERENCE

1 Report of Brantford Fluoridation Caries Study, *J. Canad. dent. Ass.*, 1954, 20, 585.

Disk Lesions and Low Backache

SIR,—It is surprising that in the long discussion on low backache in your columns so little attention has been given to the relatively common occurrence of this symptom in pregnant women. Dr. E. Schleyer-Saunders (*Journal*, February 5, p. 348) has alluded to it. We found[1] that 3.7% of 3,030 women attending the antenatal clinic of the Royal Maternity Hospital in Edinburgh suffered from this symptom in such a degree as to call for special treatment. In 60% the pain commenced before, and in 40% after, the 28th week. In general the severity of the symptoms corresponded to the degree of loosening and mobility of the sacro-iliac joints. This softening at the pelvic girdle is frequently associated with an up-and-down gliding movement at the symphysis pubis, and the amplitude of this displacement as studied radiologically gives a measure of the rocking movement at the sacro-iliac joints. With the consolidation of the pelvic joints, which occurs after delivery, the symptoms tend to subside rapidly, but in a relatively large number the backache persists.

It is generally agreed, on seemingly sound evidence, that the mobilization of the pelvic joints during pregnancy is dependent upon hormonal factors, and that the change is limited to the joints. At the same time rarefaction of the adjacent bone is common, and in two instances we have been able to demonstrate that the forcible movement at the pubic joint had resulted in a tearing away of fragments of the adjacent bone. It is quite possible that similar laminar fracture may occur at the sacro-iliac joint without being revealed by *x*-ray.

The treatment of the backache of pregnancy is relatively straightforward. Rest in bed in the majority of cases leads to rapid relief, which persists. In the occasional case rest in bed throughout the remainder of the pregnancy and the puerperium is imperative. In the rare case, in which the pain is severe and the loosening of the joints extreme, the treatment is best given in a hammock as for fracture of the pelvis. In 16 years at the Postgraduate School of London we had only three such cases; this proves its rarity. Where in the ordinary case the backache persists after childbirth, manipulation gives relief in a high proportion.

Whilst we believe that the majority of cases of low backache in pregnancy are explained as above, there are cases, as O'Connell[2] and others have shown, which depend upon a disk lesion. It may be that the endocrinal factors that determine the joint lesion may predispose to disk protrusion.—I am, etc.,

Haywards Heath, Sussex. JAMES YOUNG.

REFERENCES

1 Young, J., *J. Obstet. Gynaec. Brit. Emp.*, 1940, 47, 493.
2 O'Connell, J. E. A., *Surg. Gynec. Obstet.*, 1944, 79, 374.

SIR,—Mr. John Charnley's article on acute lumbago and sciatica in general practice (*Journal*, February 5, p. 344) is a delight to a general practitioner, perhaps most of all in the grouping of lesions and degrees of symptoms. I am particularly interested in the phenomenon that he describes as a rise of internal tension in the pulpy nucleus due to an abnormal imbibition of water accompanied by guarding spasm of the back muscles. I have the impression that I have precipitated this condition in a number of women in the menopausal phase by giving them oestrone in small doses for even a few successive days. The backache subsides slowly after withdrawal of the oestrone, which is usually prompt since irritability and lack of well-being accompany the pain, even when flushes are relieved. The type of woman affected is a water hoarder. The pain does not resemble that accompanying pelvic congestion.

Since the publication of this article, a patient has been willing to reproduce this syndrome, which had been observed to follow treatment by oestrone on three previous occasions. This woman is post-menstrual, bothered by flushes which are relieved by oestrone, and an accepted case of chronic disk lesion following an accident.

Mr. Charnley states that reasons for this watery swelling of the pulp are unknown. If other observers can confirm any relation to oestrone intake, an endocrine approach to this aspect of the disorder may be of value. The possible antagonizing effects of ethisterone or methyl testosterone obviously need consideration. It is interesting, too, to recall Dr. Cyriax's observation that low backache in women tends to be chronic, in contrast to the more acute but briefer crises in men.—I am, etc.,

London, W.2. ANNIS GILLIE.

SIR,—In his paper entitled "Spinal Disk Lesions" (*Journal*, January 15, p. 140), Dr. James Cyriax speaks of "patients with reducible displacement of part of a disk," who "abound in every hospital," and expresses his belief that such a "minor disk subluxation" can be "manipulated back into place," usually in one session.

A critical reader feels that such statements call for some elucidation. Can Dr. Cyriax substantiate his words with photographic or at least diagrammatic illustrations, to show exactly what structures are affected by the "subluxation" and the "reducible displacement of part of a disk"? It is difficult to visualize how a ruptured annulus fibrosus and herniating nucleus pulposus can be repaired in the brief ritual of a manipulation; in fact, it is a very severe strain upon the reader's credulity.—I am, etc.,

Halifax, Canada. FREDERICK W. KNOWLES.

SIR,—I am sorry to see that Mr. John Charnley has come to swim with the current on the relationship between disk disorders and "fibrositis" (*Journal*, February 5, p. 344). A theory, to become established as an axiom, must be true for every case, and judged by this standard the theory that disk trouble (I use the word to cover all the gradations of pathology Mr. Charnley describes) is responsible for "fibrositis" must fall to the ground. I am tired of hearing every conceivable abnormality laid at the door of the disk, and while I am aware that, most likely, disks are responsible for hyperthyroidism, mitral stenosis, gall stones, and pregnancy, not to mention typhoid, lupus, and worms, I do not know which disks are displaced in "fibrositis" of the occipito-frontalis, temporalis, and masseter (presumably those between the basi-splenoid and basi-occiput, or perhaps between the dens and the basi-occiput, or even between the dens and the body of C2).

I have deliberately put "fibrositis" in inverted commas because it is established beyond doubt that it is not an inflammatory lesion. But it may very well be a metabolic one which would not show under the microscope. When an unexpected demand is placed on a muscle not in training, and particularly in a reduced state of health of the patient, that muscle, as Mr. Charnley states, goes into spasm, thus restricting its own blood supply. It cannot then get rid of its metabolites and it remains in spasm until its blood supply is re-established by accurate deep friction, which traumatizes it sufficiently to produce the inflammatory response of local vasodilatation. The surrounding normal muscle-fibres must not be traumatized, of course. The same effect can often be obtained by passively stretching the muscle, hence the success, at times, of manipulation. This conception also quite easily explains the sudden onset in many cases. But I still have too great a faith in Nature's way of arranging things to believe that

the body tries to protect an internal derangement of the spine by making a few bundles of vastus lateralis go into spasm, or tensor fascia lata, or even gluteus maximus. If nature wants to protect a joint, the muscles controlling it are put into spasm, and then in no uncertain manner—not just a pencil thick (or even pencil-lead thick) fasciculus of one or two scattered areas of often unrelated muscles.

You will want proof, Sir, of my contentions, and I regret that by far the best proof I can give is to cite my own case, as I am the walking torpedo of the diskopath theory. I am still physically fit for strenuous activity of every kind (which I need not elaborate beyond saying it included Rugger till over 40), and have all my disk spaces fully maintained, in spite of having been a life-long sufferer from acute, chronic, and recurrent "fibrositis" in almost every muscle in my body, and having had both "brachial neuritis" and acute sciatica due to referred pain from trapezial and gluteal "fibrositis." The reference is proven because the massage of the areas of origin has cured the referred pain without any treatment of the spine at all. But it is a condition my 10-year-old daughter can cure for me. I look forward to the day when physiotherapists will relearn the same art, and orthopaedic surgeons and specialists in physical medicine will again come to recognize that there are more things in heaven and earth than disks.—I am, etc.,

Canterbury. F. G. ST. CLAIR STRANGE.

SIR,—May I, as another general practitioner, support the comments of Dr. R. N. R. Grant (*Journal*, February 19, p. 480) on the "disk" controversy? We all see scores of cases of fibrositis, only a small proportion of which are sent to the hospital. Most of us would agree that the syndrome is related in some way to weather, to muscular strain, and is quite certainly epidemic. It is my impression that even the muscle groups affected vary in each epidemic, one producing "lumbago" and the next affecting the shoulder girdle. Perhaps there is a relationship to Bornholm disease, in its being a specific infection.

It is very difficult to let oneself be persuaded that what is probably second only to the common cold in causing epidemic "dis-ease" is produced by mechanical disorder. —I am, etc.,

Dundee. RONALD A. B. RORIE.

SIR,—As a routine in general practice for more than 30 years, I have manipulated cases of low backache of sudden origin and have followed this with a firm bracing of the hips, back and front, with four or five strips of 3-in. (7.6-cm.) rigid zinc oxide plaster. Unless there was an allergy to rubber, this temporary corset gave support and comfort that was appreciated. It was removed after a fortnight, and then, but only if necessary, was physiotherapy advised.

The key word here is "sudden," for it eliminated most cases of gynaecological or urological origin. If there was a sciatica I ordered absolute bed rest for up to six weeks if needed, and have never withheld morphine. I have also used subcutaneous infiltration of oxygen into the buttocks, which, by forming a personal air ring, seemed to give comfort. One case required surgical aid; several, after one or two relapses, were helped by surgical belts; but the majority improved and appeared to be grateful.

Even allowing for fashion in diagnosis there does seem to have been a real increase in the occurrence of this disability in the last few years.

May the modern craze for comfort be the cause? The drawing-room of my youth is now the lounge, and the parental exhortation has changed from "Sit up straight" to "Oh, do relax." The old chairs had almost upright backs which kept the spinal muscles at the alert. No effort is required supinely to sit in the modern ultra-comfortable armchair, supporting as it does every part with soft pads of latex foam, but, in contrast to the old type, a big demand is made on over-slackened muscles to raise the body from its luxurious setting. Three of my cases of sudden low backache were caused in this way. Should the body have to adapt itself to the furniture or the furniture to the body? Is the multi-spring mattress an improvement on the firmer flock or horsehair, and is it entirely blameless?

The suggestion is that our modern luxury tends to promote a laxness in the spinal tissues which renders them increasingly liable to dislocation.—I am, etc.,

London, N.W.11. C. BERKELEY WAY.

POINTS FROM LETTERS

Experiments in Hospital

Dr. SYLVIA DICKINSON (Bristol) writes: With regard to the work done by Dr. B. Laurance at the Bristol Maternity Hospital (*Journal*, December 11, 1954, p. 1392), are any follow-up studies being made to find out whether these children subsequently react differently to infection compared with untreated children or show any other effect of the penicillin treatment in early infancy?

Trilogy

Mr. MICHAEL REILLY (Plymouth) writes: As "Fallot's tetralogy" is now so firmly ensconced in medical literature (*Journal*, January 29, p. 269), may I put forward a plea, in the interests of uniformity, that "Charcot's triad" be rechristened "Charcot's trilogy"? Triad, tetrad, pentad, and so on, have for long enough denoted mere groups of three, four, five, etc., while a cycle of four dramas, three tragic and one satiric, has for two and a half millennia been called a "tetralogy." Why not "trilogy" for Charcot's signs, which really are three tragic manifestations?

What is Health?

Dr. A. R. EATES (London, S.W.3) writes: Why do we want to know what it is? How are we to assess or measure it? . . . Health or wholeness is a harmonious development of a man's physical, mental, and moral qualities. It can only be estimated in relation to the man's environment; it must be a variable quantity. The health or fitness required of a young athlete which enables him to run 100 yards in 10 seconds is very different from that of an elderly clerk in a quiet office. Each may be equally efficient in what he sets out to do, and, so long as each can do . . . without excessive strain and with satisfaction to himself and others all the calls upon him in his day's work, each is to be classed as "healthy." Health is a relative quantity.

Medical Aspects of Professional Boxing

Dr. P. F. CASSIDY (Glasgow) writes: I have read with interest Dr. J. C. Laurie's letter on boxing (*Journal*, January 22, p. 227). I disagree that a boxer enters the ring with the object of doing damage to his opponent's cranium and its contents. He enters the ring to pit his skill and ability against an opponent, as men have done since the beginning of time. In boxing no one wishes to see unevenly matched opponents. No one who is a true lover of the sport likes to see a knock-out, because the term knock-out does not exist in true boxing parlance. Points decision is the verdict of choice. . . . In his last sentence, however, Dr. Laurie expresses the sentiments of all true lovers of the sport that "'boxing' grows on one." In this I agree, and I trust that there will always be doctors who without financial gain will give protection to those lads who, in spite of all anti-boxing advocates, continue to give pleasure to boxing lovers.

Unwrapping the "Journal"

Dr. H. LYNDHURST DUKE (Cross-in-Hand, Sussex) writes: Before you finally close this correspondence I feel you should learn of a quite unforeseen, indeed sensational, sequela, news of which I have received from a fellow member of the Association: "Re your letter 'Unwrapping the *Journal*,' I see you advise the Editor to have it 'loosely wrapped.' Two weeks ago the wrapping was delivered to me *minus* the *Journal*!"—the opposite extreme to that about which the correspondence opened and even more distracting. I can only hope the wrapper arrived in one piece and that the loss has been made good.

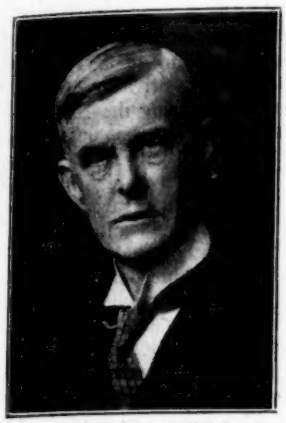
Mr. A. C. GOODWIN (Dawlish) writes: My experience differs completely from that of Dr. H. Lyndhurst Duke (*Journal*, February 12, p. 419) as I rarely (if ever) find the *Journal* so loosely rolled that I can carry out the methods he describes. I find the following procedure simple and efficacious in all cases. With the sharp point of the narrow blade of an ordinary pair of scissors I cut through the length of the outer layer of the wrapper (avoiding the exposed pages of the contents), then insert the point of the broad blade into the cut and run the blade along its whole length. The wrapper is then removed in one piece.

Obituary

Sir HENRY WADE, C.M.G., D.S.O., M.D.
F.R.C.S., F.R.C.S.Ed.

The death occurred at Edinburgh on February 21 of Sir Henry Wade, consulting surgeon to Edinburgh Royal Infirmary. He was 78 years of age.

The son of the Rev. George Wade, Henry Wade was born at Falkirk in 1877 and was educated at the Royal High School, Edinburgh, and at Edinburgh University, where he graduated M.B., Ch.B. with honours in 1898. For nearly two years after graduation he was on active service as a civil surgeon with the Royal Scots Fusiliers in the South African war and was awarded the Queen's Medal with four clasps. On his return to Edinburgh Wade became assistant to Sir William Turner in the department of anatomy in the university, and in 1903 was elected F.R.C.S.Ed. In that year he was appointed conservator of the museum of the college, and subsequently he served the college for exactly fifty years as lecturer, examiner, member of the President's council, and, from 1943 to 1953, as representative of the college on the General Medical Council. He was awarded a gold medal for his thesis when he proceeded to the M.D. in 1907.



[*Swan Watson, Edinburgh*

Wade was early appointed to the surgical staffs of Leith Hospital and Edinburgh Royal Infirmary, and was assistant surgeon there on the outbreak of the first world war in 1914, when he joined the Scottish Horse mounted brigade field ambulance and served with the unit in Gallipoli. In 1916 he was appointed consulting surgeon to the Egyptian Expeditionary Force, and for three years served in Egypt, Sinai, Palestine, and Syria. For his services with Allenby in Egypt and Palestine he was twice mentioned in dispatches, was awarded the D.S.O. in 1918, and in the following year was appointed C.M.G., receiving also the Order of the White Eagle of Serbia. On the conclusion of hostilities Wade returned to Edinburgh and resumed his appointments as conservator of the museum of the Royal College of Surgeons, lecturer in surgery in the school of medicine, and surgeon to Leith Hospital, appointments he held for 17 years. In 1924 he became surgeon-in-ordinary to Edinburgh Royal Infirmary, and remained in the active service of the hospital until he retired in 1939 as consulting surgeon. During the second world war he continued in active surgical work as consulting surgeon to Bangour E.M.S. Hospital, West Lothian. He was knighted in 1946. He was predeceased by his wife in 1929.

We are indebted to Mr. DAVID BAND for the following appreciation: Wade was a surgeon of outstanding brilliance and an enthusiastic clinical teacher. At the outset of his surgical career he devoted two years to pathology, and personally performed all post-mortem examinations on surgical cases at Edinburgh Royal Infirmary. In the post-mortem room he became interested in the changes in the upper urinary tract which accompanied prostatic obstruction, and he traced the post-operative sequelae which had led to the fatal issue. He made serial whole sections through the pelvis and prostate in the cadaver and observed the morbid anatomy of the prostate in the various age groups and at different stages of prostatic obstruction. As a result of this investigation Wade published in 1914 in the *Annals of Surgery* a profusely illustrated monograph on the surgical anatomy and pathology of the operative treatment of prostatism. The drawings in black-and-white and in colour of the entire urinary tract in prostatism demonstrated more perfectly than had before been done the effects of backward pressure on the upper urinary tract. The whole sections clearly showed that in the operation of prostatectomy enucleation of the gland had not been complete, but that the adenomatous part alone had been enucleated through a line of cleavage between it and a false capsule produced by compression of the more peripheral gland elements. These lie within the true gland capsule and, with the latter, must remain intact if the operation of enucleation of the prostate is to be performed with success. His presentation of this work made a deep impression on Hugh Hampton Young, of Baltimore, and Wade was invited by him to attend the following year in the Buchanan-Brady Institution of the Johns Hopkins Hospital, which was to be opened as a urological department. War prevented this, but in 1920 the promised visit was made and Wade remained with Young for several months.

Between the two wars Wade published some 35 papers on urological surgery. In each, advances in surgical management were described or appraised. Throughout his career as a surgeon and clinical teacher Wade insisted on attention to anatomical detail and an adequate knowledge of surgical pathology as essential qualifications in the training of a surgeon. It was the application of these principles which brought to him such a great measure of success in the surgery of urinary tuberculosis and in the treatment of vesical tumours, including a large series of cases of total cystectomy with ureterocolic anastomosis. He was one of the first to draw attention to the invasion of the renal vein by hypernephroma, and he showed in his paper in the *Australian and New Zealand Journal of Surgery* in 1935 that in nephrectomy for tumour the renal vein could be ligated with safety between its junction with the vena cava and the limit of neoplastic invasion. His collection of serial whole sections of renal pathology was unique, and he always maintained that the radiographic appearances obtained by retrograde pyelography must be correlated with a detailed study of the pathological changes in the kidney. He held no brief for pyelographic anomalies which might be listed as due to faulty technique.

During his 15 years as chief in the Royal Infirmary Wade attracted to his operating theatre and his ward a steady stream of visiting surgeons from overseas. His Saturday morning lectures and demonstrations became an outstanding example of postgraduate instruction at its best. He travelled by invitation to America and Australia, and was awarded the honorary Fellowships of the American College of Surgeons in 1930, the Royal Australasian College of Surgeons in 1935, and the Royal College of Surgeons in Ireland in 1939. It was his forthright support of all that was genuine in surgical progress which led to his election to the most exclusive surgical societies of the English-speaking world, including membership of the International Association of Surgeons and Fellowship of the Los Angeles Surgical Society. In 1932 he delivered the Ramon Guiteras lecture on the balanced urinary system before the American Urological Association, of which he was elected an honorary member. He was elected a Fellow of the Royal Society of Edinburgh in 1932, he was President of the Royal College of Surgeons of Edinburgh from 1935 to 1937, and he was elected an honorary Fellow of the Royal College of Surgeons of England in 1943 and of the Royal Society of Medicine in 1951.

His years of active surgical progress behind him, Wade devoted his energies to help in the formation of the National Health Service, and he became a convener of many committees in connexion with the services of the South-eastern

Regional Hospital Board in Scotland. He was a strict disciplinarian in every surgical service under his control, but there was another side to his nature. He was a student of social and natural history and was widely read in the literature of these subjects. His Harveian Oration on "Harvey in Scotland" in 1938 and his Thomas Vicary lecture before the Royal College of Surgeons of England on "The Barber Surgeons of Edinburgh" in 1949 record the diligence of his researches and his erudition. A member of the British Medical Association for over 50 years, Wade served as a vice-president of the Section of Surgery when the Association held its Annual Meeting at Edinburgh in 1927. He was a member of the Representative Committee in 1943–4, the Negotiating Committee from 1944 to 1949, and the Evidence Committee in 1947–8. He was also a member of the Medical Planning Commission.

At his country home of Pilmuir, Haddington, East Lothian, Wade had acquired and preserved an old house and garden in the Scottish baronial style. His favourite flowers were the rare primulas, and the habits of the nesting birds were observed from year to year, as many had been expertly ringed. The versatility of his interests brought to Wade a humanity and a wealth of understanding which were reflected in the lifelong friendships he made at home and abroad with all who came to know him—surgical colleagues or patients, historians or pupils.

OSWALD T. AVERY, M.D.

Dr. Oswald T. Avery, the distinguished bacteriologist, died in Nashville, Tennessee, on February 20, after a long illness.

Oswald Theodore Avery was born in Halifax, Nova Scotia, on October 21, 1877, and qualified in medicine from the College of Physicians and Surgeons, Columbia University, where he graduated M.D. in 1904. After a few years in general practice Avery was appointed associate director, department of bacteriology, Hoagland Laboratory, in 1907, a position which he left to become an assistant in the hospital department of the Rockefeller Institute for Medical Research. Here Avery began the studies on the pneumococcus with which his name will always be associated, and was one of the founders of immunochemistry. He discovered and identified the capsular polysaccharides of type III pneumococcus and demonstrated their function. He also separated the polysaccharide antigens. Avery remained at the Rockefeller Institute until his retirement in 1943, when he became a member emeritus. His writings chiefly concerned the biological activities, immunological characteristics, and pathogenic properties of the pneumococcus. This work was recognized in the award of the Kober Medal by Georgetown University Medical School in 1946, and in a Lasker Award by the American Public Health Association in 1947. Elected a foreign member of the Royal Society in 1944, Avery received its Copley Medal in 1945. He also received the Paul Ehrlich Gold Medal (1933) and the New York Academy of Medicine Medal (1944). He was Mickle Fellow, University of Toronto, in 1946. McCall University awarded him an honorary LL.D. degree in 1935, and he was an honorary member of the Pathological Society of Great Britain and Ireland.

Dr. S. D. ELLIOTT writes: Many have commented upon the similarities between Dr. O. T. Avery and Sir Frederick Gowland Hopkins. To some extent they were alike in appearance as well as in personality; both through their classical researches had a profound influence upon biological science; and both left an indelible impression on the minds of the young people who were privileged to work in association with them. Dr. Avery always disclaimed any ability to assess from a single interview the potentialities of applicants for the coveted honour of a place in his laboratory. Yet it is remarkable how many of those who worked with him at the hospital of the Rockefeller Institute achieved distinction. The explanation, in part at least, lay in his capacity to transmit to others his own way of thinking; this, in the recipient, yielded its own ultimate harvest. Few of those who knew Dr. Avery will hear of his passing without deep emotion. His gay charm, great wisdom, and lovable character combined to make in him a unique personality. He was indeed a prince among scientists. "Good night, sweet prince."

Sir CHARLES J. MARTIN, C.M.G., D.Sc., LL.D. D.C.L., M.B., F.R.C.P., F.R.S.

The obituary of Sir Charles Martin was printed in last week's *Journal* at p. 543. We are indebted to Dr. W. R. AYKROYD, director of the nutrition division of the Food and Agriculture Organization of the United Nations, for the following appreciation:

Many will feel a sense of loss on learning of the death of Sir Charles Martin. I had personally the privilege of working under him in the Lister Institute during the last years of his directorship in the late 'twenties. He was unfailingly kind to young research workers, and was always ready to help in clearing up their problems. He would turn from whatever he was doing—and he was always engaged in some research activity of his own—his eyes would glitter behind his spectacles, the keen incisive mind would come into operation like a smooth-running machine—and one had one's answer. No one who worked with him will ever forget his quick, illuminating comments on detailed technical questions or on the broader aspects of science. His own scientific papers were always beautifully written, and he would go to endless trouble in showing beginners how to present their scientific results and in editing their efforts. At the same time he distrusted words divorced from solid fact. I shall never forget one incisive remark, "You write too easily. That's a dangerous gift." I think that his old pupils, when undertaking some task in later years, often asked themselves, "What would Sir Charles think of this?" His influence is hard to define; it stemmed perhaps from a rare combination of unpretentiousness, honesty, and remarkable intellectual gifts. But such words somehow fail to convey what "Sir Charles" meant to those who were privileged to know him and the respect and affection which we felt for him.

The untimely death on January 10 of Dr. DONALD P. DOW has removed an outstanding personality and reduced the number of medical men whose work has left its mark on India. He was 49 years of age. Donald Peter Dow was born at Ardrossan, Ayrshire, and was educated at Airdrie Academy and at St. Mungo's and Anderson Colleges, Glasgow, qualifying by taking the Scottish triple qualification in 1930. After qualification he held the appointments of house-physician and house-surgeon at Dumfries and Galloway Royal Infirmary, and he then practised for short periods in various parts of the United Kingdom before going to India to pursue his studies at the School of Tropical Medicine, Calcutta. Dr. Dow was brought up a Baptist and always had a leaning towards the mission fields. He applied to several churches for this kind of work, but his state of health caused them to reject his applications. In 1934—when he married Miss Esther Wells at Bombay—he persuaded the Methodist Missionary Society to appoint him medical superintendent of the Victoria Leprosy Hospital at Dichpali, Hyderabad, and from then until he returned to Scotland in 1944 he devoted much time to the improvement of the facilities of the institution, particularly in connexion with the sanitary arrangements and the electricity supply, eventually building up a modern leprosarium. While at the hospital he saw the accommodation for inmates increase from 400 to 850. He also became lecturer in leprosy in Osmania University, conducting clinical courses for students

and postgraduates at Dichpali. Dr. Dow was the first missionary to become a member of the Hyderabad State Medical Council, and a final recognition of his work and worth came with the award of the Nizam's jubilee medal. During his stay in India Dr. Dow wrote extensively, his publications including lecture notes on leprosy and articles on leprosy research—he came to be regarded as an authority on leprosy—and on occupational therapy, the psychological approach, pellagra, and on other subjects. In 1944 ill-health compelled him to return to Scotland, and in the following year he established himself in practice at Newtyle, Angus, where he became widely known as a "beloved physician." A devout Christian, Dr. Dow could hold his own in theological circles, and his services as a preacher and speaker were much in demand at Strathmore and beyond. Many people derived encouragement from his logic, enthusiasm, and example. Fees he received as a preacher went to help the work of the Mission to Lepers or to augment the church funds—acts of generosity and remembrance which endeared him to a still wider circle. At the time of his death he was a member of the Angus Executive Council, a lecturer to the local branch of the Red Cross and examiner in first aid, president of the Dundee Auxiliary of the Mission to Lepers, and he attended patients at the Church of Scotland Eventide Home at Belmont Castle and the Newtyle Home for the Blind. He was a founder member of the College of General Practitioners and president-elect of the Dundee Branch of the British Medical Association. He is survived by a widow and two adopted children.

Dr. A. P. NUTTALL died on February 19 at his home at Rickmansworth, Hertfordshire, to which he had retired for family reasons 25 years ago. He was 85 years of age. Arthur Peel Nuttall was born on May 20, 1869, and was educated at the Bury Grammar School, at Rossall, and at Owens College, Manchester, from which he went to University College Hospital to complete his medical course. He graduated M.B.(London) in 1893, proceeding to the M.D. in the following year. After holding house appointments at University College Hospital (including the post of house-physician to his fellow Lancastrian Sir Thomas Barlow), he returned to his birthplace, Bury, where he joined his father in practice. When his father retired in 1905 Dr. Nuttall took over the practice until his own retirement. He became one of Bury's most respected and most successful practitioners. He was honorary surgeon to the Bury Infirmary from 1909 to 1926, when he was made honorary consulting surgeon. In his younger days Dr. Nuttall was a keen Volunteer. He was always proud of the fact that he had held the office of surgeon-major to the 5th battalion of the Lancashire Fusiliers (T.) in the days before the R.A.M.C. was constituted. He was also very proud of the honorary membership of the British Medical Association which was conferred upon him in his old age. While in retirement he was always ready to help his colleagues in Rickmansworth during periods of pressure, and he led, in fact, a very active life. His wife, formerly Miss Dorothy May Stead, died in 1953. He leaves two daughters.

Dr. G. M. ADDISON died suddenly at his home at Westgate-on-Sea on January 30 at the age of 52. George Montagu Addison was born on November 13, 1902, and was educated at Haileybury College, where he gained a science scholarship to Pembroke College, Cambridge. He went on to St. Thomas's Hospital for his clinical training and qualified M.R.C.S., L.R.C.P. in 1927, taking the degrees of M.B., B.Chir. in the following year. In 1929 he obtained the D.P.H. of the English Royal Colleges. After qualification he completed a number of hospital appointments, and then his interests turned to general practice. After practising for a time in London and Staines he went to Westgate-on-Sea in 1934. During the second world war he served in the R.A.M.C. from 1940 to 1945, through the Alamein campaign of 1941–3, and then in Europe from 1944 to 1945, attaining the rank of major. For most of his service he was employed as a hygiene officer, and in the spring of 1945 he was appointed a deputy assistant director of hygiene. After the war he returned to Westgate, where, in addition to the work of his practice, he was medical officer to St. Cecilia's Musicians Convalescent Home, the Salvation Army Eventide Home, St. Michael's Convalescent Home, and to various schools. He was also divisional surgeon to the St. John Ambulance Brigade and on the panel of the Ministry of Pensions and National Insurance. A former secretary of the Margate Medical Society, he was also secretary of the East Kent Division of the British Medical Association from 1936 to 1939. He was chairman of the standing committee of the chamber of commerce in Westgate at the time of his death.

Dr. W. G. SUTCLIFFE writes: Anyone who knew George Addison could not have failed to be impressed by his high moral integrity and his devotion to his profession. He had a keen sense of humour, and many will remember his happy way of cheering a dull meeting with his wit. He was not concerned with popular favour and never feared to express what he felt to be right. He showed great courage during the past year when, knowing his precarious state of health, he cheerfully continued to work and to support his family. He will be greatly missed in Thanet. Every sympathy is extended to his widow and to his two sons and eight daughters.

By the tragic death of Dr. LAWRENCE HENSHAW in an aeroplane accident on February 5 Nigeria has lost a particularly well loved citizen. Lawrence Michael Eken Richard Henshaw, who was born at Calabar in 1898, was educated at the Sacred Heart School there and at King's College, Lagos. He then acted as a dispenser for a time, work which helped him later when he went to Edinburgh University as a medical student. At Edinburgh he was one of a group of fellow Nigerians, many of whom have since made notable contributions to medical work in Nigeria. He graduated M.B., Ch.B. in 1927, and in the following year obtained the additional qualifications of L.M. and D.T.M.&H. before returning to Nigeria in 1928. He was employed as a member of the Nigerian Medical Service from the time he returned to his home country until 1952. Two years after he joined the Service he was granted the title of medical officer, a status which to-day would be given on entry, and in 1948 he was promoted to senior medical officer. Four years later he retired from Government service and became medical officer to the Palmol estate, near Calabar. He was appointed an honorary O.B.E. in the Birthday Honours of 1948.

We are indebted to Dr. CARMICHAEL WILSON for the following appreciation: It would be impossible to find anyone who was more popular with and more respected by all who knew him than Lawrence Henshaw, and he was known to many. As a colleague he was staunch and helpful and kind to all, no matter who they were. As a friend he could not be bettered, while his quiet joviality was a tonic to everyone, whether in hospital, at meetings, or in the home. His sterling worth and sound sense were well recognized, and he had been appointed to the governing body of the new University College Hospital at Ibadan. He was returning home from a meeting of the governing council of the Nigerian College of Arts, Science, and Technology, of which he was also a member, when he met his death. Nigeria and the Commonwealth have lost a very fine citizen who will be deeply mourned by his many friends, and not least by me.

McK. McC. writes: Colonel GEORGE A. MOORE, whose obituary was published in the *Journal* of February 19 (p. 485), was a keen and capable soldier. I first met him as D.D.M.S. of the divisions west and south of Armentières. We of the 40th division had come up from south of Arras after the great German attack of March, 1918, and were put into the front at Fleurbaix next to the Portuguese division. He knew were were to be attacked and probably driven back, and wisely prepared us all for this eventuality. The attack was not long in coming, but, thanks to Colonel Moore's

admirable administration, our losses were not heavy, though our right flank was in the air with the enemy between the ambulances and our own front line. After his retirement from the Service in 1921 he opened his house in Redcliffe Square, S.W.10, as a surgery and took up general practice. His paternal outlook on everyone endeared him to his patients, who worshipped him. During the air raids the sirens were a call to him to open his surgery and prepare tea for all of his patients who cared to come. The fearful moments were less fearful to them because of his bravery, generosity, and real Christian affection. One of his great loyalties was to all Irish graduates in and around London. He had been president of the Irish Medical Schools and Graduates Association in 1934 and continued to serve on the council, the meetings of which he rarely failed to attend. His last attendance was two days before he died. He will be missed by many of his former patients in the Redcliffe Square area, where his tall and erect soldier-like figure was so well known. He will never be forgotten by those who knew him, because of his constant charitable benevolence to his fellow men and women.

The obituary of Mr. PHILIP TURNER was printed in last week's *Journal* at p. 545. A. E. S. writes: Mr. Philip Turner was a great gentleman; quiet, somewhat shy, and always courteous. I learned from him as a dresser at Guy's. His surgery was anatomical and with minimum trauma. In later years I often saw him at the Hornsey Central Hospital. Once I met him unexpectedly in the Grand Hotel, Sheffield. He was held in respect and affection by all.

Mr. R. AFFLECK GREEVES writes: Having been privileged to diagnose and treat Lieutenant-Colonel G. E. Malcomson's eye trouble, to which Lieutenant-General Sir Ernest Bradfield refers in his appreciation (*Journal*, February 19, p. 483), I should like to correct a misapprehension on Sir Ernest's part. What Colonel Malcomson suffered from was not a retinal detachment but a bilateral paracentral choroiditis, which cleared up after the elimination of oral sepsis, leaving him with perfect central vision in one eye and slightly reduced visual acuity in the other.

Medico-Legal

MEDICAL REPORTS IN LITIGATION

[FROM OUR MEDICO-LEGAL CORRESPONDENT]

On October 1, 1954, sweeping amendments in the procedure of the High Court were brought into force in order to make a start in implementing the recommendations of the Evershed Committee. These are aimed at reducing the cost of litigation. Broadly speaking, Masters of the Supreme Court were given much wider powers than they had hitherto enjoyed to ensure the exclusion before an action reaches the stage of trial of all unnecessary expense in properly defining what is at issue between the parties, and in preparing the evidence on both sides which will be necessary for the decision of that issue at the trial.

In cases in which medical evidence is required, Masters were empowered to order at the hearing of the summons for directions that a medical report should be agreed if possible, and, if not, that the number of medical witnesses to be called by each party should be restricted. It has of course been and will remain a common practice for joint medical examinations to be made and joint medical reports to be used in litigation if there is no real difference of opinion between the doctors advising both sides, and the joint report can by agreement then be used in evidence without either side's doctor being called.

The scope of the Master's new powers in this respect was recently discussed in the Court of Appeal in the case of *Worrall* v. *Reich*.[1] That was an action for damages for personal injuries, and on the summons for directions the Master ordered: "Exchange medical reports; if not agreed, the medical evidence be limited to two witnesses for each party." This order was upheld by Mr. Justice Glyn Jones in chambers.

On appeal to the Court of Appeal it was decided that the order, in so far as it directed the exchange of medical reports, was invalid in that they were documents made on behalf of either party on the advice of their legal advisers in preparation for the trial and therefore privileged from disclosure. Although in some circumstances it might be desirable from the practical point of view that medical reports should be exchanged, and although it might be highly expedient that the parties should adopt that course by agreement in many cases, it could not properly be made the subject of an order.

DEATH FROM PINK DISEASE

A verdict of accidental death from pink disease was recorded on February 22 at Stoke-on-Trent on an 11-months-old baby boy. The coroner, Mr. G. W. Huntbach, said that the disease was due, not as at first thought to teething powders, but to legally prescribed grey tablets (hydrarg. cum cret.).

The baby had been healthy until about November, 1954, when he was said to have had teething trouble. The father bought some teething powders. These were Steedman's new type of powder and were shown to contain no mercury. On January 13, 1955, Dr. A. G. Mowat, the family doctor, prescribed 12 tablets of hydrarg. cum cret. because the child had a slight digestive disorder, irritability, and pains in the head, and from January 14 for the next six days the mother administered 2 tablets a day to the baby in accordance with instructions. The baby got no better, and on January 26 was admitted to hospital suffering from pink disease. After improving somewhat, the baby became restless and pyrexial on February 2 and died on February 3.

At necropsy the liver was found to show slight fatty degeneration, the kidneys on both sides contained granular casts, and both lower lungs were congested. Chemical analysis carried out by Mr. F. L. Cann, of the West Midland Forensic Science Laboratory, showed that a specimen of kidney contained 500 μg. of mercury, a liver specimen 130 μg., and a brain specimen 40 μg. Dr. C. Giles, consultant pathologist at the City General Hospital, confirmed the necropsy findings and agreed that death was from pink disease due to the ingestion of mercury.

DEATH FROM SENSITIVITY TO AMETHOCAINE

[FROM OUR MEDICO-LEGAL CORRESPONDENT]

On January 17, 1955, Thomas Traynor, a ship's cook aged 62, was admitted to Broadgreen Hospital, Liverpool, for chest investigations for suspected bronchial carcinoma. He was also suffering from a peptic ulcer. On February 10 he was to have had a bronchogram carried out. He was given an amethocaine lozenge to suck, to indicate whether or not he was allergic to amethocaine. As he showed no reaction, half an hour later as a preliminary to undertaking the bronchogram his throat was sprayed with ½ to 1 ml. of amethocaine solution. During this procedure he suddenly collapsed, had a convulsive fit, and died within three minutes.

At the inquest held by the Liverpool City Coroner on February 12 the pathologist at Broadgreen Hospital, Dr. Francis Whitwell, gave evidence that in his opinion death was caused by convulsions due to sensitivity to amethocaine, and that there was no satisfactory test for hypersensitivity. Sections of the deceased's lungs showed that bronchial carcinoma was in fact present.

[1] [1955] 2 *Weekly Law Reports*, 338.

Medical Notes in Parliament

PEACEFUL USES OF ATOMIC ENERGY

A motion introduced by Mr. RONALD BELL (South Buckinghamshire, Con.) on February 25 gave M.P.s an opportunity to express their hopes of the benefits to be gained from the peaceful application of atomic energy, and the use of radioactive isotopes in research, medicine, industry, and agriculture. All those who spoke shared Mr. Bell's purpose, to turn public attention to beneficial developments which had been going on unnoticed in the shadow of the great bomb explosions.

The first anxiety that was expressed was about the shortage of scientific man-power; it was said that the existing atomic programme could absorb the total output of physics graduates from British universities for several years. And the first satisfaction was that there would be no sulphurous fumes from the atomic fission generators of electric power. There was also general agreement on safety: the new atomic power stations to be built were inherently safe; the reactors could not run away and turn into junior atomic bombs, as some people seemed to fear.

Mr. BERNARD BRAINE (Billericay, Con.) questioned whether sufficient money was being spent on research, particularly in comparison with what the United States was doing. He suggested that there was a strong case for examining the finance provided for medical research in such matters as radiation sickness. The budgets of the Medical Research Council and the Ministry of Health were stretched to the uttermost. He urged that financial help should be given directly to this very special and expensive research.

Disposal Problems Solved

Mr. NIGEL BIRCH, Minister of Works, had to devote much of his reply to questions that had been asked about the £300m. capital investment programme for nuclear power stations. But on safety matters he was able to say that the most stringent precautions were taken—some people thought them too stringent—and the record had been extraordinarily good. Great advances were being made in the disposal of radioactive waste. The method depended on the degree of radioactivity; some went into the air, some was piped out to sea, some was taken in steel or concrete containers and dumped 1,000 miles out at a depth of 2,000 fathoms, and some of the very dangerous stuff had to be stored. There were some waste products, such as stronthium^{90} and caesium^{137}, that were particularly dangerous, but techniques were being evolved to put them to useful work. Caesium, for example, could be used for medical purposes. The point was that this was a manageable problem. If all electricity in the country was produced from nuclear power the dangerous products would amount to only one or two tons a year. There really was no danger, and the natural fears of the unknown that had been aroused were unnecessary.

"HORROR COMICS" BILL

The Children and Young Persons (Harmful Publications) Bill got its second reading on February 22, after some severe buffeting in debate. It is one of those measures of which all approve the end but many have serious doubts about the means chosen to ensure them, and substantial alterations will be proposed during the committee stage. No one disputed the basis on which the Home Secretary presented the Bill, to make special provision for the protection of children and young persons against the depraving effects of "horror comics." But there was vigorous criticism of the failure to deal with the whole law of obscenity in literature, on the lines suggested by the Society of Authors, instead of introducing this piecemeal measure, and serious doubts were expressed that even so its language was so wide as to endanger publishers and printers. It was apparent from the debate that in the subsequent stages efforts will be made to limit the duration of the Bill, so that its effects shall not continue and be liable to misuse after the reasons for its introduction had disappeared; to secure that all prosecutions taken under it should be with the assent of the Director of Public Prosecutions, in order to avoid the confusion caused by different benches of magistrates taking widely different views on the extent to which pictures might tend to corrupt children; and to define more explicitly the element of intent.

Cadmium Poisoning Report

Mr. HAROLD WILSON (Huyton, Lab.) asked the Minister of Labour on February 24 what machinery existed for ensuring that the deaths through cadmium poisoning of workers employed at copper refineries were reported to the department, and whether he was satisfied that the machinery resulted in the notification of all such deaths. Mr. HAROLD WATKINSON, Parliamentary Secretary, said that any death resulting from acute cadmium poisoning at premises under the Factories Acts would be notifiable as an accident in accordance with those Acts, and satisfactory machinery existed for such notification. The question of ill effects from long-continued exposure to small amounts of cadmium was being carefully studied in the light of the recent report prepared by a member of the staff of the Medical Research Council and other available evidence both positive and negative. Mr. WILSON said the reason some of the deaths were not reported was that the disease was not generally known about. He had obtained no fewer than six certificates from registrars showing cadmium poisoning to be the cause of death, and these had not been notified to the Ministry. Mr. WATKINSON said that if Mr. Wilson would let him have the evidence it would be considered in conjunction with Dr. Bonnell's report, which was being given the most urgent attention.

Lead Poisoning Among Children

Dr. BARNET STROSS (Stoke-on-Trent, Central, Lab.) questioned the Minister of Health about lead poisoning occurring among children, and whether the public appreciated the danger of using paint containing lead on woodwork that children might handle. He also sought information about the deaths of two children in Manchester Children's Hospital. Miss PAT HORNSBY-SMITH, Parliamentary Secretary, replying on February 21, said that such cases were not notifiable. There were 11 deaths among children ascribed to lead poisoning in the five years ending September, 1954. Of the seven deaths from 1952 to 1954 none was reported as showing signs of lead encephalopathy; information was not available for the other deaths. Serious danger arose only when in rare cases a child developed a peculiar appetite for chewing articles containing lead which resulted in cumulative poisoning. Lead paint had been the most frequent reported cause, apart from one recent outbreak due to the use of old battery cases as fuel on domestic fires. One of the two children who died in the Manchester Hospital was stated to have chewed furniture and toys and the source of poisoning was paint; information on the second case could not be obtained. The Department had issued notes to a number of widely read journals suggesting that their readers should be warned of the danger, particularly when repainting furniture or walls, and the Minister was glad of this further opportunity of making known this occasional hazard.

Tuberculosis in Immigrants

Mr. SOMERVILLE HASTINGS (Barking, Lab.) asked the Minister of Health on February 21 what precautions were taken to ensure that immigrants from Ireland and elsewhere were not carriers of infectious pulmonary tuberculosis, and what inquiries were made to ascertain whether such immigrants had or had not been inoculated against this disease. Mr. IAIN MACLEOD stated that every person, British or alien, coming to this country was subject to the ordinary health control at the port of entry. An alien immigrant was in addition examined by a medical inspector of aliens; if tuberculosis was discovered or suspected, the medical inspector would issue a certificate to that effect and permission

to land would normally be refused. Citizens of the Republic of Ireland were not aliens. The answer to the second part of the question was "None."

Radiation Hazards in Industry

Mr. HAROLD DAVIES (Leek, Lab.) asked the Minister of Labour on February 24 what steps he was taking to study and limit radiation hazards in the health of workers exposed to ionizing radiations, and whether he would consult the Minister of Fuel and Power about the occupational health problems that might arise as a result of the programme of nuclear power development. Mr. HAROLD WATKINSON, the Parliamentary Secretary, stated that the precautions taken at factories to protect workers from ionizing radiations were carefully watched by the Inspectorate of Factories, which was notified by the Atomic Energy Authority of all consignments of radioisotopes supplied by them to factories. The Chief Inspector had also issued an advisory booklet on *Precautions in the Use of Ionizing Radiations in Industry*. He was considering, in consultation with the Chief Inspector, whether, in addition to the general requirements of the Factories Acts, more detailed special regulations would be desirable for factories using ionizing radiations. In all such matters he had the benefit of the expert advice of a radiological advisory panel, of the statutory advisory committee appointed under the Radioactive Substances Act, 1948, and of the Atomic Energy Authority itself. He was in consultation with the Minister of Fuel and Power regarding the measures that would be necessary for the protection of the health of the workers in the projected atomic power stations.

Civil Estimates

The Vote on Account for 1955–6 presented to Parliament on February 21 shows that expenditure on the National Health Service is estimated at £463,370,000, an increase of £24m. over the previous year.

Harley Street Cable.—The POSTMASTER-GENERAL said that he very much regretted the inconvenience caused to telephone subscribers in the Harley Street and Wimpole Street area. The Post Office had had to replace a section of a large cable which was in a very bad condition. By working day and night the job was finished in three weeks. They did all they could to minimize interruptions, but were seeing if it was possible in such cases to give subscribers a better system of warning.

Chiropody.—Mr. MACLEOD said that he would like to see a chiropody service available for all who would benefit from it, but financial considerations at present rule out any extension of the existing limited facilities.

Thames Pollution.—The very extensive technical investigations into the causes of pollution of the River Thames of the Water Pollution Research Laboratory have been completed. The results are being analysed; and it is hoped that in the next few months they will be ready for consideration by the departmental committee of the Ministry of Housing and Local Government.

Silicosis Claims.—In 1953 the Silicosis Medical Board dealt with 465 applications under the Workmen's Compensation Acts for certificates of death in respect of coal-miners; in 330 of these cases it was certified that death was due to silicosis or pneumoconiosis and in 135 cases it was certified that death was not due to the disease.

Universities and Colleges

UNIVERSITY OF ST. ANDREWS

The following candidates have been approved at the examinations indicated:

M.D.—Mrs. D. Avril J. Oatway (with commendation), B. O. Igwebe.

M.B., CH.B.—Sheila E. Cheong, J. S. Cook, J. L. Crichton, Rene Dattner, P. A. E. Edmundson, J. G. McDonald, Anne M. MacGillivray, A. J. Mackenzie, J. A. C. Macmillan, Yvonne D. Symon, A. R. Taylor, Anne M. Thomson, Mrs. Sheila K. Tod, T. H. E. Woods.

UNIVERSITY OF LONDON

The following have been nominated for appointment as representatives of the University on the governing bodies indicated in parentheses: Professor C. G. Rob (St. Mary's Hospital); Mr. J. D. S. Flew (University College Hospital); Mr. D. K. Mulvany (Laycock Secondary School); Professor J. M. Mackintosh (London School of Economics and Political Science); Dr. E. R. Boland (General Medical Council).

Professor W. J. Hamilton has been appointed a representative of the Board of Preclinical Studies on the Board of Advanced Medical Studies, in place of Professor J. Whillis.

Professor J. A. C. Knox has been appointed a member of the Special Advisory Board in Dietetics, Nutrition, and Household Science.

The following have been recognized as teachers of the University in the subjects indicated in parentheses: *Institute of Obstetrics and Gynaecology*, Dr. A. E. Claireaux (Pathology). *Guy's Hospital Medical School*, Dr. P. J. Collard (Pathology), Dr. J. C. Houston (Medicine). *London Hospital Medical College*, Dr. J. R. Ellis (Medicine). *St. George's Hospital Medical School*, Dr. C. W. Kesson (Children's Diseases). *King's College*, Dr. J. L. Mackinnon (Anatomy). *Middlesex Hospital Medical School*, Dr. J. D. N. Nabarro (Medicine), Dr. Margaret D. Snelling (Radiology). *Royal Dental Hospital of London School of Dental Surgery*, H. M Pickard, F.D.S., M.R.C.S., L.R.C.P. (Dental Surgery). *St. Mary's Hospital Medical School*, Dr. P. H. Sanderson (Medicine).

UNIVERSITY OF WALES

The following degrees were conferred in Congregation on January 22:

M.B., B.CH.—Inez Davies, W. J. Evans, R. Griffith, Margaret D. James, J. R. Lewis, H. K. Lloyd, O. McCann, V. J. Nash, B. L. P. Nelson, Jeanine Olsen, H. V. Price, I. P. Vaughan, R. N. Wade, C. G. Young.

UNIVERSITY OF BIRMINGHAM

Dr. K. H. Ginzel has been appointed Senior Research Fellow in Neuropharmacology in the Department of Experimental Psychiatry from April 1, 1955, and Dr. J. Williams Lecturer in Anatomy from July 1, 1955.

Mr. D. M. Morrissey resigned his appointment as Lecturer in Surgery on December 31, 1954.

The first line of the seventh paragraph under the heading "University of Birmingham" in the *Journal* of December 11, 1954 (p. 1428), should read "The title of University Clinical Tutor has been conferred," instead of University Clinical Lecturer.

The following degrees were conferred in Congregation on December 17, 1954:

PH.D. IN THE FACULTY OF MEDICINE.—Deirdre M. Edward.

M.B., CH.B.—Yaw Asirifi, P. H. Astill, Joyce E. Bailey, Patricia A. Bramley, J. Bullock, E. P. C. Hadley, Olga R. Harbron, Ella E. L. Hot, J. W. P. Jarrams, D. Learmont, A. P. Mayne, E. T. Melley, W. K. Merifield, K. Middleton, J. D. Nicholas, P. A. North, L. J. T. Pearson, A. Sutherland, Elizabeth M. Tilsen, D. Wright, R. A. Yeomans.

SOCIETY OF APOTHECARIES OF LONDON

The following candidates, having completed the final examination, have been granted the diploma of L.M.S.S.A.:

R. N. Wade, P. M. Gurrin, P. Jago, F. R. F. Dibb, T. Freüchen, A. P. Brown, E. A. Capell, D. A. Bennett, J. E. Todd, J. A. Bradford.

The following candidates have been awarded the Diploma of Master of Midwifery:

A. P. Camilleri, S. Miller.

The following candidates have been awarded the Diploma in Industrial Health:

Z. Khan, W. H. Suffield.

ROYAL COLLEGE OF OBSTETRICIANS AND GYNAECOLOGISTS

At a meeting of the Council of the College held on January 29, with the President, Sir Arthur Gemmell, in the chair, Professor B. P. Watson was appointed William Meredith Fletcher Shaw Memorial Lecturer for 1955.

The following were elected to the Membership of the College:

R. H. O. Bannerman, D. Barron, H. R. C. Benny, D. B. Brown, T. I. Cope, A. C. Coulthard, K. D. Drayton, W. A. W. Dutton, B. A. Gavourin, H. S. Gavourin, T. S. Ghosh, A. P. B. Harston, B. O. Howie, Beryl M. Joles, M. Konar, Wendy E. Lewington, J. D. Llywelyn-Jones, Philippa M. Ludlam, C. F. Macdonald, J. G. Mathie, A. A. M. Mendis, D. Methuen, Catherine H. Mitchell, N. G. Mukherjee, R. N. Nag, Chiew Seng Oon, S. Prodhan, R. T. Scars, H. B. Sinha, D. H. K. Soltau, O. S. Treisman, Yin-Kai Tsao, J. K. Tully, J. A. M. Van Belkum.

The following have been awarded the Diploma in Obstetrics:

L. C. Steindel, D. C. Wilkins.

FACULTY OF RADIOLOGISTS

At the examination for the Fellowship of the Faculty held in November, 1954, the following satisfied the examiners:

Radiodiagnosis.—R. G. Britt, S. Davis, J. G. Duncan, R. G. Grainger, J. B. Hearn, J. W. Laws, H. F. March, L. L. Ralph, W. Stachurko.

Radiotherapy: E. W. Emery, H. G. Frank, R. W. Gunderson, P. B. Kunkler, K. A. Newton, T. M. Prossor.

INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **February 12** (No. 6) and corresponding week 1954.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the 160 great towns in England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES in Countries and London	1955					1954				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	14	1	8	0	1	11	0	7	2	3
Dysentery	1,110	53	310	1		669	100	186	6	3
Encephalitis, acute	2	0	1	0		1	0	3	0	
Enteric fever:										
Typhoid	1	0	1	0		0	0	0	0	2
Paratyphoid	4	0	3	0		4	0	1	0	
Food-poisoning	94	15		0		109	12		0	
Infective enteritis or diarrhoea under 2 years				10	15				15	21
Measles*	18,363	1945	258	599	94	1,849	16	52	28	356
Meningococcal infection	24	2	9	2	4	40	2	11	2	2
Ophthalmia neonatorum	30	1	2	0		27	3	5	0	
Pneumonia†	1,156	68	313	56	5	931	38	252	10	
Poliomyelitis, acute:										
Paralytic	9	2	1	0	1	15	2	4	0	6
Non-paralytic	7	1				6	1			
Puerperal fever§	251	39	8	2		280	38	13	2	
Scarlet fever	746	54	104	51	21	1,161	44	202	39	27
Tuberculosis:										
Respiratory	767	89	140	20		787	70	117	33	
Non-respiratory	85	8	27	4		117	4	33	3	
Whooping-cough	2,065	137	259	67	36	1,916	76	366	74	34

DEATHS in Great Towns	1955					1954				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	0	0	0	0	0	1	0	0	0	0
Dysentery	0	0		0		1	0		0	
Encephalitis, acute		0			0		0			0
Enteric fever	0	0	0	0		0	0	0	0	
Infective enteritis or diarrhoea under 2 years	9	0	0	0	1	13	0	4	1	1
Influenza	84	12	8	4	2	41	8	6	0	3
Measles		0	0	0	0		0	0	0	0
Meningococcal infection		2	0				1	1		
Pneumonia	387	58	41	19	7	495	74	30	8	15
Poliomyelitis, acute	0	0			1	0	0			0
Scarlet fever		0	0	0	0		0	0	0	0
Tuberculosis:										
Respiratory	107	15	17	3	7	133	6	22	2	5
Non-respiratory		1	2	1	1		0	0	0	0
Whooping-cough	3	1	0	0	0	0	0	0	0	0
Deaths 0–1 year	230	24	29	7	16	297	27	37	7	25
Deaths (excluding stillbirths)	6,652	956	713	173	217	7,982	1207	747	147	243
LIVE BIRTHS	7,446	1099	862	202	357	7,756	1154	899	221	413
STILLBIRTHS	188	24	25			228	24	23		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Vital Statistics

Influenza

In the great towns of England and Wales 82 deaths from influenza were recorded in the week ending February 19. This total was 2 fewer than the previous week's. 42 deaths were recorded in Greater London, compared with 29 in the previous week, making the highest weekly total this winter.

Industrial Accidents and Diseases

The number of workpeople (other than seamen) in the United Kingdom whose deaths from accidents in the course of their employment were reported in January was 109, compared with 120 in the previous month and 132 in January, 1954.

The number of cases of industrial diseases in the United Kingdom reported during January, 1955, were as follows: lead-poisoning 2, compressed air illness 2, epitheliomatous ulceration 18, chrome ulceration 20; total 42.

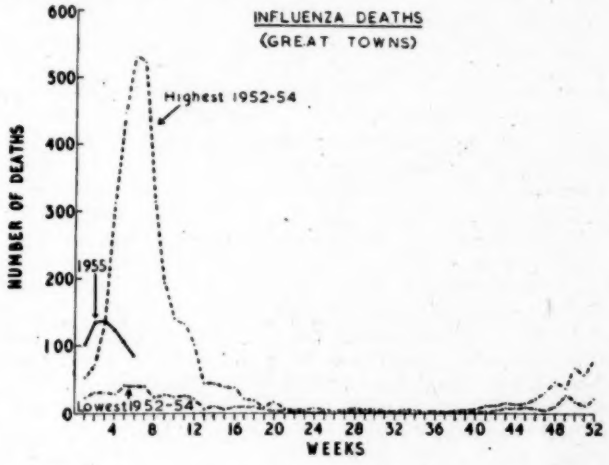
There was one death from epitheliomatous ulceration, due to mineral oil.—*Ministry of Labour Gazette*, February, 1955.

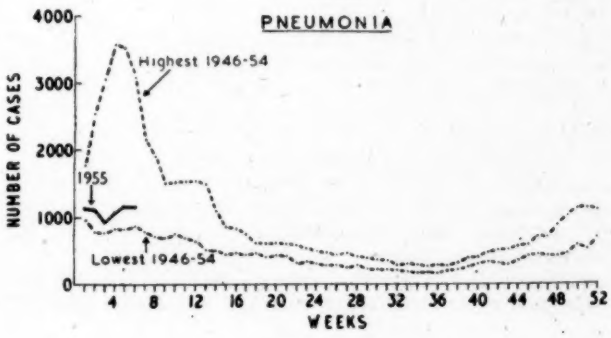
Week Ending February 19

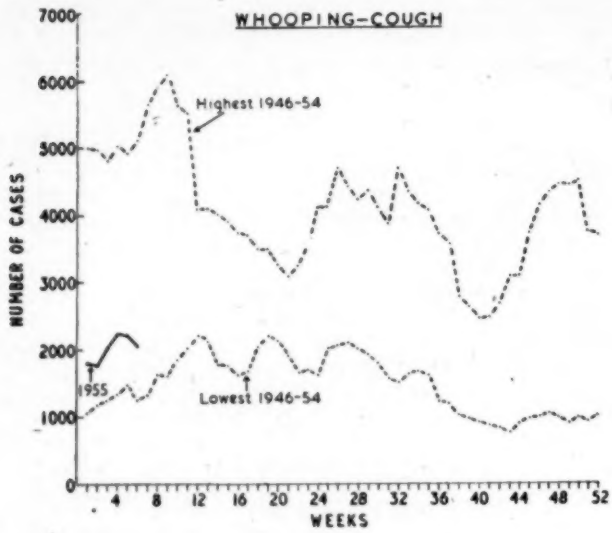
The notifications of infectious diseases in England and Wales during the week included: scarlet fever 682, whooping-cough 1,910, diphtheria 16, measles 19,976, acute pneumonia 1,020, acute poliomyelitis 21, dysentery 1,145, paratyphoid fever 3, and typhoid fever 4.

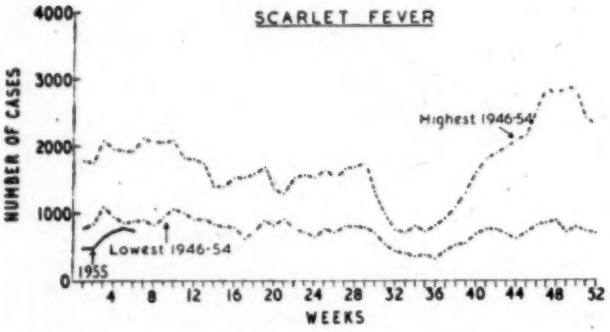
Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases (deaths for influenza) of certain diseases notified weekly in England and Wales (great towns for influenza). Highest and lowest figures reported in each week during the nine years 1946–54 (influenza 1952–4) are shown thus ------, the figures for 1955 thus ———. Except for the curves showing notifications in 1955, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.









Infectious Diseases

The largest variations in the notifications of infectious diseases in England and Wales during the week ending February 12 were increases of 5,634 for measles, from 12,729 to 18,363, and 131 for dysentery, from 979 to 1,110, and decreases of 148 for whooping-cough, from 2,213 to 2,065, and 45 for scarlet fever, from 791 to 746.

The largest rises in the incidence of measles were 1,018 in Yorkshire West Riding, from 1,853 to 2,871, 824 in Lancashire, from 2,453 to 3,277, 650 in London, from 1,295 to 1,945, 308 in Nottinghamshire, from 667 to 975, 299 in Northumberland, from 291 to 590, 268 in Essex, from 560 to 828, 250 in Cheshire, from 646 to 896, 247 in Derbyshire, from 531 to 778, 239 in Warwickshire, from 576 to 815, 216 in Durham, from 565 to 781, 212 in Middlesex, from 241 to 453. The largest falls in the local trends of whooping-cough were 36 in Warwickshire, from 133 to 97, 35 in Kent, from 137 to 102, and 30 in Essex, from 95 to 65. The only large decline in scarlet fever was 20 in Lancashire, from 126 to 106. 16 cases of diphtheria were notified, being 2 fewer than in the preceding week. 5 of the 14 cases of diphtheria were notified in Kingston-upon-Hull C.B. 16 cases of acute poliomyelitis were notified, and these were 3 more for non-paralytic and the same for paralytic cases as in the preceding week. The largest returns were London 3 and Middlesex 3 (Willesden M.B. 2).

The largest increases in the local outbreaks of dysentery during the week were Lancashire 93, Northampton 43, and Durham 34. The largest returns were Lancashire 461 (Oldham C.B. 128, Blackpool C.B. 94, Blackburn C.B. 73, Manchester C.B. 66, Stretford M.B. 20, Blackburn R.D. 10), Yorkshire West Riding 79 (Sheffield C.B. 29, Leeds C.B. 28), Durham 76 (Ryton U.D. 20, Durham R.D. 11), London 53 (Shoreditch 11), Northamptonshire 52 (Northampton C.B. 31, Kettering M.B. 17), Norfolk 48 (Norwich C.B. 29), Suffolk 40 (Woodbridge U.D. 33), Northumberland 37 (Newcastle-upon-Tyne C.B. 20), Glamorganshire 35 (Cardiff C.B. 14), Leicestershire 34 (Leicester C.B. 32), Lincolnshire 27 (Scunthorpe M.B. 15), Cheshire 26 (Stockport C.B. 14), Nottinghamshire 24 (East Retford M.B. 15), and Yorkshire North Riding 20 (Middlesbrough C.B. 19).

Medical News

World Population.—Since 1930 the population of the world has risen by 30%, according to estimates in the 1954 *United Nations' Statistical Yearbook*. In mid-1953 it stood at between 2,459 and 2,634 million, with a density of about 49 to the square mile (19 per sq. km.). These figures include an allowance of a little over 200 million, apparently, for the population of the U.S.S.R. The estimates of the populations of the individual continents (*excluding figures for the U.S.S.R.*) also include the densities. In persons per square mile (figures per sq. km. in parentheses), these were: Europe, 212 (82); Asia, 132 (51); North and South America, 20 (8); Africa, 17 (7); Oceania, 5 (2). The estimates of the continental populations (*again excluding the U.S.S.R.*) in descending order of magnitude are given as: Asia, 1,288–1,439 million; Europe, 400–404 million; North and South America, 347–355 million; Africa, 199–216 million; Oceania, 13.8–14.2 million.

Medical Man-power.—The news of the appointment of the committee under Mr. HENRY WILLINK, Q.C., to investigate Britain's medical man-power (*British Medical Journal*, February 26, p. 548) has provoked some immediate, anxious comment. Mr. ARTHUR BLENKINSOP, M.P., Parliamentary Secretary to the Ministry of Health in the last Labour Government, in a letter to *The Times*, is concerned that the committee should keep before it "the great need for a further reduction in the size of general-practitioner lists." He expresses surprise that the Government should even be "contemplating any form of restriction of entry into a profession," and notes the absence on the committee of "any representation of the public interest." The *Irish Times*, on the other hand, has been quick to see a possible threat to Irish doctors. "If a decision is taken in Britain to limit entry to the medical faculty," says the paper in an article on February 23, "a big problem will arise in the placing of Irish doctors, many of whom find openings in Britain."

Princess Louise Children's Hospital.—On February 24 the board of governors of St. Mary's Hospital decided to adopt the recommendations of their co-ordinating subcommittee on the conversion of the Princess Louise (Kensington) Hospital for Children to adult use (see *Journal*, January 29, p. 299). Two days earlier at a meeting held by the Kensington and Hammersmith Division of the B.M.A. and open to all members of the profession in these areas the following resolution had been passed unanimously by the 30 doctors present:

"Being satisfied as to the continuing needs of the sick children in the area, the medical practitioners of the Kensington and Hammersmith boroughs ask the Minister of Health to give serious consideration to the necessity for the Princess Louise Hospital to continue as a children's hospital serving the needs of the local population. We would further like to impress on the Minister that these needs should take priority over the teaching requirements of the St. Mary's Hospital Group."

This resolution was sent to the Minister of Health. It was also unanimously adopted by a meeting of the medical staff of the Princess Louise Hospital, which drew attention to similar resolutions passed by the council of the Royal Borough of Kensington and the Hammersmith Borough Council. The medical staff further deplored the proposed disbandment of the training school for children's nurses, "of which there are few in the country." In a statement the board of governors of St. Mary's say that they decided to inform the Minister of Health of their resolution only after giving careful consideration to the observations of

their standing committees and the Academic Board of St. Mary's Hospital Medical School, and to the representations of the borough councils of Kensington and Hammersmith.

Linstead Report.—The full text of the "Linstead Report"—in other words the report of a subcommittee of the Ministry of Health's Standing Pharmaceutical Advisory Committee of which Sir HUGH LINSTEAD, F.P.S., M.P., was chairman—was published on March 3 (H.M.S.O., price 2s. net). The report deals with the Hospital Pharmaceutical Service. The terms of reference were to review the Service and advise on its most efficient and economical organization. The committee's recommendations were summarized in the report of the Central Health Services Council for 1953, published last July (see *British Medical Journal*, July 17, 1954, p. 146), but the present report, besides rehearsing the arguments which led to the recommendations, includes the comments on it of both the Central Health Services Council itself and the Standing Pharmaceutical Advisory Committee. The report has been adopted by both these bodies (subject to some reservations by individual members of the Standing Advisory Committee), and its recommendations on the place of the pharmaceutical department in the individual hospital, group organization, staffing and accommodation, and research have been accepted by the Minister; the remaining recommendations are stated to be "under consideration." The only medical member of the Linstead committee was Dr. JANET AITKEN.

Sheffield University.—The title of reader in forensic medicine has been conferred on Dr. GILBERT FORBES, senior lecturer in charge of the Department of Forensic Medicine. Dr. O. G. DODGE has been appointed lecturer in pathology. At the Jubilee Degree Congregation on June 29, the honorary D.Sc. of the University will be conferred on Lord ADRIAN, P.R.S.

Medical Research Council.—By an Order of the Committee of Privy Council for Medical Research, Mr. RICHARD FORT, M.P., has been appointed a member of the Medical Research Council in the vacancy created by the retirement of Mr. RICHARD WOOD, M.P.

Professor J. B. Duguid, professor of pathology at Durham University, who since January has been in Jamaica lecturing at the University College of the West Indies under the Commonwealth University Interchange Scheme, has now gone on to Colombia for a fortnight on behalf of the British Council.

Dr. Albert Schweitzer has been appointed by the QUEEN an honorary member of the Order of Merit. The only other living honorary foreign member is President Eisenhower.

News in Brief.— On February 24 the DUKE OF NORTHUMBERLAND opened a 4-million-volt linear accelerator unit at the Newcastle General Hospital costing a total of £65,000. The North of England Council of the British Empire Campaign contributed the cost of the building, which amounted to nearly £27,000.

At the Glasgow Royal Maternity and Women's Hospital on February 25 the COUNTESS OF ELGIN AND KINCARDINE opened a new £100,000 Out-patient Department.

The March issue of *Family Doctor* is now available.

COMING EVENTS

Institute of Dermatology, London.—Exhibition on benign tumours of the skin, March 4–25.

Harveian Lecture of the Harveian Society of London.—On March 7, at 8.15 pm., at the Royal College of Surgeons, Professor CLARENCE CRAFOORD will lecture on "The Diagnosis and Treatment of Intra-auricular Septal Defects." Open to all interested.

Faculty of Radiologists.—Postgraduate week-end course at the Royal College of Surgeons, Lincoln's Inn Fields, March 19 and 20. Applications for enrolment (12s. 6d.) before March 12 from the Secretary of the Faculty, 45, Lincoln's Inn Fields, London, W.C.2.

Watson-Williams Memorial Lecture.—Mr. R. SCOTT STEVENSON will lecture on "The New Outlook in Otolaryngology" at Bristol University on March 8 at 8.30 p.m.

Oxford University Medical Society.—Annual Ball at Oxford Town Hall on March 11, 9 p.m. to 3 a.m. Double tickets (two guineas) from Mr. ALAN LOWER, New College, Oxford.

William Sheen Memorial Lecture.—Sir GEOFFREY JEFFERSON will lecture on "The Aneurysms of the Cavernous Sinus" at the Reardon Smith Lecture Theatre, Cardiff, on March 16 at 8 p.m.

Oliver-Sharpey Lectures. — Professor W. MELVILLE ARNOTT will lecture on "Order and Disorder in Pulmonary Function" at the Royal College of Physicians of London at 5 p.m. on March 17 and 22.

C.M.F./M.E.F. Army Physicians' Reunion.—Tenth annual dinner at Simpson's-in-the-Strand on April 2. Information from the honorary secretary, Dr. A. WILLCOX, 59, Harley Street, London, W.1.

British Occupational Hygiene Society.—Conference on "The Assessment of Health and Disease in Industry" at the London School of Hygiene and Tropical Medicine on April 4 at 11 a.m. Details from Dr. D. G. HARVEY, M.R.C. Laboratories, Holly Hill, Hampstead, London, N.W.3.

NEW ISSUES

Archives of Disease in Childhood.—The new issue (Vol. 30, No. 149) is now available. The contents include:

CONGENITAL DEFECTS IN THE PELVIC PARASYMPATHETIC SYSTEM. Orvar Swenson.
HIRSCHSPRUNG'S DISEASE IN THE NEONATAL PERIOD. Th. Ehrenpreis.
INTESTINAL OBSTRUCTION IN THE NEWBORN. H. H. Nixon.
PERITONITIS IN THE NEONATAL PERIOD. P. P. Rickham.
ACUTE INTUSSUSCEPTION IN CHILDHOOD. R. B. Zachary.
CONGENITAL DEFORMITIES OF MECHANICAL ORIGIN. Denis Browne.
CONGENITAL DEFORMITIES OF THE ANUS AND THE RECTUM. Denis Browne.
THE CARDIO-OESOPHAGEAL SYNDROME IN CHILDHOOD. Isabella Forshall.
TWO CASES OF OESOPHAGEAL STRICTURE IN CHILDHOOD REQUIRING RESECTION. R. H. Franklin and I. D. Henderson.
ACUTE DISTENSION OF THE GALL BLADDER IN CHILDREN. William Rankin.
A SURGICAL AND BIOCHEMICAL STUDY OF A CASE OF BILATERAL HYDRONEPHROSIS AND HORSESHOE KIDNEY. John Black and Joan Wagner.
SACRO-COCCYGEAL TERATOMA. James Lister.
CONGENITAL PYLORIC STENOSIS IN OLDER BABIES. John Rendle-Short and R. B. Zachary.

Issued six times a year; annual subscription £3 3s.; single copy 12s. 6d.; obtainable from the Publishing Manager, B.M.A. House, Tavistock Square, London, W.C.1.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Monday, March 7

HARVEIAN SOCIETY OF LONDON.—At Royal College of Surgeons of England, 8.15 p.m., Harveian Lecture by Professor C. Crafoord (Stockholm): Diagnosis and Treatment of Intra-auricular Septal Defects.
INSTITUTE OF PSYCHIATRY.—5.30 p.m., Dr. E. Stengel: Lecture-demonstration.
OXFORD UNIVERSITY MEDICAL SOCIETY.—At Radcliffe Infirmary, 8.15 p.m., Dr. F. E. Camps: The Notting Hill Murders.
POSTGRADUATE MEDICAL SCHOOL OF LONDON.—4 p.m., Professor M. Arnott: Fever in Disease.
UNIVERSITY COLLEGE LONDON: DEPARTMENT OF BIOCHEMISTRY.—At Physiology Theatre, 4.45 p.m., Dr. Joseph Needham, F.R.S.: New Light on Physico-Chemical Aspects of Morphogenesis.

Tuesday, March 8

●BRISTOL UNIVERSITY.—8.30 p.m., Patrick Watson-Williams Memorial Lecture by Mr. R. Scott Stevenson: New Outlook in Otolaryngology.
CHELSEA CLINICAL SOCIETY.—At Rembrandt Hotel, S.W., 8.30 p.m., discussion to be opened by Dr. Neville Gorton, D.D., Rt. Rev. the Lord Bishop of Coventry, and Dr. E. E. Claxton, Assistant Secretary, B.M.A.: Divine Healing and the Medical Profession.
INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. Phyllis Wade: Radiotherapy of Skin Cancers, Part I.
LONDON UNIVERSITY.—At Meyerstein Lecture Theatre, Westminster Medical School, 5.30 p.m., special university lecture in biochemistry by Academician W. A. Engelhardt (Moscow): Mechano-Chemistry of Muscle.
MEDICAL SOCIETY OF LONDON.—At Claridge's, 7.30 for 8 p.m., annual dinner.
MEDICAL WOMEN'S FEDERATION: SCOTTISH EASTERN ASSOCIATION.—At Pharmacology Lecture Theatre, Teviot Place, Edinburgh, 8.30 p.m., film by Professor Ian Aird: Separation of Conjoined Twins.
ST. MARY'S HOSPITAL MEDICAL SCHOOL.—At Wright-Fleming Theatre, 5 p.m., Dr. James Walker: Postmaturity and Foetal Anoxia.
WEST END HOSPITAL FOR NEUROLOGY AND NEUROSURGERY.—5.30 p.m., Mr. J. Minton: Ocular Manifestations in Clinical Neurology (Part I).

Wednesday, March 9

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. R. W. Riddell: Mycotic Infections of Subcutaneous Tissues.

INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—5.30 p.m., Dr. I. Friedmann: Pathology of Otitis Media: Experimental and Human (1).

INSTITUTE OF UROLOGY.—4.30 for 5 p.m., Mr. F. R. Kilpatrick: Tuberculosis of the Renal Tract.

LONDON UNIVERSITY.—At Physiology Theatre, University College, 5.30 p.m., special university lecture in physiology by Dr. C. R. Skoglund (Stockholm): Functional Organization of Spinal Interneurones.

NOTTINGHAM MEDICO-CHIRURGICAL SOCIETY.—8.30 p.m., Mr. J. H. Doggart: Ocular Manifestations of Systemic Disease.

OXFORD UNIVERSITY.—At Radcliffe Infirmary, 5 p.m., Litchfield Lecture by Professor C. A. Wells: Experimental Approach to Surgical Problems.

ROYAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE.—3.30 p.m., Dr. Dorothy Makepeace: Some Medical Aspects of Child Care.

ROYAL SANITARY INSTITUTE.—2.30 p.m., Dr. W. G. Patterson and Dr. S. L. Wright: Co-operation Between Local Health Authorities and the Hospital Service—Possibilities and Actualities.

ST. MARYLEBONE HOSPITAL FOR PSYCHIATRY AND CHILD GUIDANCE.—5.30 p.m., Dr. E. A. Bennet: Selection of Patients for Psychotherapy.

Thursday, March 10

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. Phyllis Wade: Radiotherapy of Skin Cancer, Part II.

LIVERPOOL MEDICAL INSTITUTION.—8 p.m., Mr. D. H. Young: Surgical Aspects of Male Infertility; Mr. F. C. Dwyer: Suppurative Arthritis of the Hip-joint in Childhood.

LONDON UNIVERSITY.—At Senate House, 5.30 p.m., special university lecture in pharmacy by Professor P. Karrer (Zurich): Curare—Alkaloids.

ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5 p.m., Hunterian Lecture by Professor G. Causey: Place of the Vascular Supply in Fatigue and Regeneration of Peripheral Nerve.

ROYAL EYE HOSPITAL.—5.30 p.m., Dr. T. H. Whittingham: Some Aspects of Refraction Work: (3) Refraction Work: Our Tools and Apparatus.

ST. ANDREWS UNIVERSITY.—At Physiology Department, Medical School, Small's Wynd, Dundee, 5 p.m., Dr. W. C. Swanson: Review of Carcinoma of the Breast in the Eastern Region.

ST. GEORGE'S HOSPITAL MEDICAL SCHOOL.—5 p.m., Dr. D. J. Williams: neurology demonstration.

WHITTINGHAM HOSPITAL.—At Archway Wing, 8.15 p.m., Dr. L. F. Hewitt: Bacterial Viruses and Heredity.

Friday, March 11

●INSTITUTE OF DERMATOLOGY.—5.30 p.m., clinical demonstration by Dr. B. F. Russell: Benign Tumours of the Skin.

INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., clinical demonstration by Dr. J. Smart: Bronchitis.

INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—3.30 p.m., Dr. I. Friedmann: Basis of Chemotherapy in E.N.T. Disease.

LONDON UNIVERSITY.—(1) At Physiology Theatre, University College, 5.30 p.m., special university lecture in physiology by Dr. C. R. Skoglund (Stockholm): Functional Organization of Spinal Interneurones. (2) At Senate House, 5.30 p.m., special university lecture in pharmacy by Professor P. Karrer (Zurich): Curare—Alkaloids.

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—4 p.m., Dr. W. G. Oakley: Peripheral Vascular Disease.

ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5 p.m., Urology Lecture by Mr. D. S. Poole-Wilson: Treatment of Tumours of the Bladder.

●ROYAL FACULTY OF PHYSICIANS AND SURGEONS OF GLASGOW.—5 p.m., Dr. Thomas Anderson: Antibiotics.

ROYAL MEDICAL SOCIETY, Edinburgh.—8 p.m., Valedictory Address by the Senior President.

SOCIETY OF MEDICAL OFFICERS OF HEALTH: WELSH BRANCH—At Park Hotel, Cardiff, 7 for 7.30 p.m., annual dinner.

Saturday, March 12

KENT PAEDIATRIC AND CHILD HEALTH SOCIETY.—At Queen's Head Hotel, Maidstone, 3 p.m., Presidential Address by Dr. P. R. Evans: Baby Farming.

APPOINTMENTS

BROWN, R. J. K., M.B., B.Chir., M.R.C.P., D.C.H., Senior Lecturer, Department of Child Health, Welsh National School of Medicine, Cardiff.

EAST ANGLIAN REGIONAL HOSPITAL BOARD.—J. R. Thompson, M.Chir., F.R.C.S., Consultant Surgeon, Peterborough and Stamford Hospital Group; R. E. B. Tagart, M.Ch., F.R.C.S., Consultant Surgeon, Newmarket General Hospital; G. C. Foster-Smith, M.R.C.S., L.R.C.P., D.A., Assistant Anaesthetist, Norfolk and Norwich Hospital Group; J. Littlejohn, L.R.C.P.&S.Ed., and Dorothea M. Norman-Jones, M.B., B.Chir., D.P.H., D.P.M., Registrars in Psychiatry, Fulbourn and Addenbrooke's Hospitals; Joan McConnell, M.B., B.Chir., Registrar in Psychiatry, St. Andrew's Hospital, Norwich; R. H. V. Ollendorff, M.R.C.S., L.R.C.P., Registrar in Psychiatry, Ipswich Mental Hospital Group; A. K. Mitra, F.R.C.S., Orthopaedic Registrar, East Suffolk and Ipswich Hospital and Ipswich Borough General Hospital; Elizabeth L. Brown, M.B., Ch.B., Medical Registrar, Nayland Sanatorium; W. S. Grove, M.B., B.Chir., Medical Registrar, Foxhall Hospital, Ipswich; J. C. S. Ainley-Walker, B.M., B.Ch., D.A., Anaesthetic Registrar, United Norwich Hospitals; Kathleen M. McNamara, L.R.C.P.&S.I., Anaesthetic Registrar, Peterborough Memorial Hospital and Annexes; J. A. Scanlon, M.B., B.S., Anaesthetic Registrar, West Suffolk General Hospital.

FRANKLIN, J. A. C., M.B., B.S., D.P.H., Deputy County Medical Officer of Health and Deputy Principal School Medical Officer, Essex County Council.

GREGO, THOMAS JAMES MYLES, O.B.E., M.B., B.Ch., Regional Medical Officer, with the Welsh Board of Health for duty in South-west Wales Area.

HILL, EILEEN E., M.B., Ch.B., M.R.C.P., Paediatric Registrar at Churchhill Hospital, Headington, Oxford.

KINGSTON-UPON-HULL HEALTH DEPARTMENT.—R. G. Davies, M.D., D.P.H., Deputy Medical Officer of Health and Deputy Principal School Medical Officer for the City and County of Kingston-upon-Hull, Deputy Medical Officer of Health (at Hull) to the Hull and Goole Port Health Authority and Medical Inspector of Aliens under that Authority; Margaret I. Hendrie, M.D., D.P.H., D.C.H., D.Obst.R.C.O.G., Senior Medical Officer for Maternity and Child Welfare for the City and County of Kingston-upon-Hull.

LIVERPOOL REGIONAL HOSPITAL BOARD.—Jane I. Gibson, M.B., Ch.B., Consultant Pathologist to Birkenhead and North Wirral Groups; B. H. McGuirk, M.R.C.S., L.R.C.P., F.F.A. R.C.S., D.A., Part-time Consultant Anaesthetist for Chester and Wirral Areas; C. H. de Boer, M.B., B.Chir., F.R.C.S., M.R.C.O.G., Part-time Consultant Obstetrician and Gynaecologist to Liverpool Maternity Hospital, the Women's Hospital, and Warrington General Hospital (appointed jointly with United Liverpool Hospitals).

MACKENZIE, A. C., M.D., D.P.H., Medical Officer of Health for Borough of Shrewsbury and member of staff of Salop County Medical Officer of Health.

NORTH-WEST METROPOLITAN REGIONAL HOSPITAL BOARD.—A. P. H. Randle, M.R.C.P.I., D.Phys.Med., Consultant in Physical Medicine, Garmon Manor and Mid-Herts and Luton and Hitchin Groups; J. A. Robertson, M.B., M.R.C.P., Consultant General Physician, Brentford Hospital and Teddington, Hampton Wick, and District Hospitals; S. Davis, M.B., M.R.C.P., D.M.R.D., Consultant Radiologist, Royal Northern Hospital, Wood Green and Southgate Hospital, and Highlands Hospital; Barbara E. Woodhead, M.B., M.R.C.P., D.P.H., D.P.M., Consultant Psychiatrist, Tavistock Clinic; H. H. G. Eastcott, M.S., F.R.C.S., Consultant in General Surgery, St. Mary's Hospital and the North-west Metropolitan Regional Hospital Board (Paddington General Hospital) (joint appointment); Cecily F. Statham, M.B., B.S., D.R.C.O.G., D.A., Assistant Anaesthetist (S.H.M.O.), Royal Northern Hospital; R. R. Wilson, M.D., Consultant in Morbid Anatomy, North-western Group Laboratory; M. J. Gilkes, M.B., F.R.C.S., Consultant Ophthalmologist, Royal London Homoeopathic Hospital; I. F. K. Muir, M.B., F.R.C.S., Consultant in Plastic Surgery, West Middlesex Hospital and the Regional Centre for Plastic Surgery and Jaw Injuries, Mount Vernon Hospital; O. Garrod, M.D., M.R.C.P., Consultant Physician, Barnet General Hospital; E. E. Bullock, L.M.S.S.A., D.Phys.Med., Assistant Physician in Physical Medicine (S.H.M.O.), Edgware General Hospital; H. F. Lunn, M.B., F.R.C.S., Senior Casualty Officer (S.H.M.O.), Watford Peace Memorial Hospital; M. F. Hart, M.D., M.R.C.P., Assistant Physician in Physical Medicine (S.H.M.O.), Mount Vernon Hospital and Northwood, Pinner and District Hospital.

ROADS, P. G., M.D., D.P.H., Deputy Medical Officer of Health, County Borough of Sheffield.

SOUTH-WESTERN REGIONAL HOSPITAL BOARD.—A. F. Barnett, M.D., M.R.C.P., Senior Medical Registrar to Plymouth Clinical Area; A. Gordon, M.B., Ch.B., Registrar to Department of Pathology at Frenchay Hospital, Bristol; D. de G. Villet, M.B., Ch.B., F.R.C.S., Surgical Registrar at Gloucestershire Royal Hospital, Gloucester; G. A. Cutler, M.B., B.S., Registrar in Obstetrics and Gynaecology to Bath Group of Hospitals; G. R. Fearnley, M.D., M.R.C.P., Consultant Physician to North Gloucestershire Clinical Area; E. R. Jones, M.R.C.S., L.R.C.P., D.P.M., Assistant Psychiatrist at Mendip Hospital, Wells.

UNITED LEEDS HOSPITALS BOARD.—A. E. Wall, M.Sc.Physiol., M.B., Ch.B., F.R.C.S., Consultant Assistant Surgeon in Department of Neurosurgery, United Leeds Hospitals, and Consultant Neurosurgeon in hospitals under control of Leeds Regional Hospital Board; J. A. Aylwin, M.B., Ch.B., F.R.C.S., Consultant Assistant Surgeon in Department of Thoracic Surgery, United Leeds Hospitals, and Consultant Thoracic Surgeon in hospitals under control of Leeds Regional Hospital Board. Both part-time appointments.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Davidson.—On February 21, 1955, to Dorothy (formerly Harpur), wife of Arthur S. Davidson, M.B., F.R.C.S.Ed., D.L.O., of Cranleigh Road, Kettering, Northants, a son.

Dixon.—On February 23, 1955, in Cardiff, to Megan, wife of Dr. J. M. S. Dixon, a son.

Gee.—On February 8, 1955, at Stoke-on-Trent, to Doreen, wife of Dr. C. Gee, a brother for Michael.

Lecutier.—On February 22, 1955, at the Duke of York Home, Bradford, Yorks, to Angila, wife of E. R. Lecutier, F.R.C.S., a son—Philip Edmond.

DEATHS

Blackman.—On February 19, 1955, at Malvern, Worcs, Geoffrey Gordon Barham Blackman, M.B., B.Chir.

Bowes.—On February 11, 1955, at St. Catherine's Nursing Home, Bath, Richard Frederick Butlin Bowes, M.R.C.S., L.R.C.P., of Fiveway House, Batheaston, Bath, Somerset.

Brown.—On February 26, 1955, at Green Garth, Yealand Conyers, near Carnforth, Lancs, Edward Vipont Brown, M.D., formerly of Manchester, aged 92. Memorial service at Friends Meeting House, Mount Street, Manchester, March 8, 1.20 p.m.

Bruce.—On February 14, 1955, at Budleigh Salterton, Devon, Olliver Bruce, M.R.C.S., L.R.C.P., aged 74.

Edwards.—On February 5, 1955, at his home, The Antlers, Rathdown, Co. Wicklow, Geoffrey Dixon Edwards, M.B., B.Ch., aged 62.

Gilbart-Smith.—On February 3, 1955, in a nursing home, Thomas Bewley Gilbart-Smith, M.R.C.S., L.R.C.P., of Fountain House, Crowborough, Sussex, aged 79.

Hatcher.—On December 19, 1954, at Greenbank Hospital, Plymouth, Devon, Georgina Roberts Hatcher, M.B., Ch.B.

Hay.—On January 29, 1955, at 25, Aglionby Street, Carlisle, James William Hay, M.B., Ch.B., aged 56.

Humby.—On February 2, 1955, at Lymington, Hants, Daniel Morgan Humby, M.R.C.S., L.R.C.P., L.D.S.

Lewis.—On February 4, 1955, at 5, Hamboro Gardens, Leigh-on-Sea, Essex, Arthur Daniel Lewis, M.R.C.S., L.R.C.P., formerly of Stoke Newington, London, N., aged 81.

MacGibbon.—On February 5, 1955, in hospital, Stranraer, Wigtownshire, George MacGibbon, M.B., C.M., of 1, Windsor Terrace, Academy Street, Stranraer.

Mackenzie.—On February 2, 1955, Donald William Morison Mackenzie, M.B., Ch.B., Lieutenant-Colonel, R.A.M.C., retired, of Piltdown, Sussex.

Mackinnon.—On February 3, 1955, at 2, Herriet Street, Pollokshields, Glasgow, Mary Jessie Mackinnon (formerly Macdonald), M.B., Ch.B., of Portree, Isle of Skye.

MacRae.—On February 4, 1955, in Devizes Hospital, Donald Mackenzie MacRae, C.B.E., M.D., of Southbroom Cottage, Devizes, Wilts.

Robinson.—On February 11, 1955, at 1, Coombe Rise, Kingston-upon-Thames, Surrey, Richard Deane Robinson, D.S.C., M.B., B.S., aged 48.

Semple.—On February 1, 1955, at the home of his son, Kintallon, Kilmacolm, Renfrewshire, Henry Frederick Semple, M.R.C.S., L.R.C.P., of Sandown, Exmouth, and Budleigh Salterton, Devon.

Shaw.—On February 11, 1955, at Morchard Cottage, Hardingstone, Northampton, Emily Helen Shaw, M.D., wife of Dr. Eric H. Shaw.

Any Questions ?

Correspondents should give their names and addresses (not for publication) and include all relevant details in their questions, which should be typed. We publish here a selection of those questions and answers which seem to be of general interest.

Export of Drugs

Q.—*Are there any restrictions on the drugs that (a) a doctor or (b) a patient may take with him out of this country for use abroad?*

A.—No export duty is chargeable on goods leaving the United Kingdom. Information about the duties and restrictions on goods taken or imported into other countries may be obtained from the Board of Trade, Export Services Branch, Lacon House, Theobalds Road, London, W.C.1 (Tel. CHAncery 4411). The exportation from the United Kingdom of drugs restricted by the Dangerous Drugs Acts and Regulations made thereunder is prohibited unless authorized by a licence issued by the Home Office Drugs Branch, Whitehall, London, S.W.1, from which department full information concerning licences and the regulations can be obtained.

Certain other drugs—that is, those specified in Group 13 of the Export of Goods (Control) (Consolidated) Order, 1954 (S.I. 1954 No. 118), as amended—may not be exported without licence from the Board of Trade, Export Licensing Branch, Atlantic House, Holborn Viaduct, London, E.C.1. Notwithstanding the provisions of this Order, however, licences are not required for reasonable quantities of such drugs which a passenger proceeding overseas might be expected to carry with him or include in his unaccompanied luggage for his own regular and private use. Additionally, a doctor proceeding overseas will be permitted to take with him or include in his unaccompanied baggage without licence reasonable quantities of such drugs as are intended for his professional use abroad. It is to be noted, however, that special regulations apply to the exportation of drugs to China, Hong Kong, Macao, Tibet, and North Korea, and the concession does not apply in respect of these destinations.

Rorschach Testing

Q.—*What is the Rorschach test? How is it performed, what does it measure, and how reliable is it?*

A.—If a large irregularly shaped blot of ink is made on a piece of paper, which is then folded so that the blot is pressed between two sides of paper, and the paper is then opened out again, a complexly shaped pattern with bilateral symmetry is seen. The Rorschach test forms provide a series of such shapes, photographically reproduced from originals made many years ago. The subject is asked to look at them and to imagine meaningful figures in them if he can. His responses are recorded, and are subsequently interpreted by the aid of fixed rules.

Three classifications of the responses are made, by: (1) location—that is, responses to the whole or to a part of the pattern, to the dark part of the pattern or to the white part between; (2) content of what is visualized—that is, human or animal, or man-made objects, or landscapes or maps; (3) determinant—that is, responses to shading, texture, colour (three of the patterns are coloured), responses involving the feeling of movement, etc. The results of the whole of scores based on these classifications are then recorded in a profile, which is used, together with other observations, for diagnosis. Thus numerical ratios between responses of two kinds are considered of diagnostic value for some purposes. The skilled interpreter believes he is able to provide conclusions, both of a general and a particular kind, about (1) normal balance, (2) general personality structure, (3) intellectual aspects, (4) emotional aspects, (5) clinical aspects. Under the latter heading the Rorschachist claims to be able to diagnose organic disease of the brain, neurosis, depression, mania, schizophrenia. As an example, organic disease is indicated by a low number of responses of poor quality, schizophrenia by many poor "whole" responses.

There can be no doubt that such a test procedure must elicit a large amount of information, and that the skilled interpreter, especially if he is using the test as part of a guided interview, can derive valuable insight into a number of aspects of the personality. The fixed forms by which interpretation is supposed to proceed have, however, never been validated; and properly conducted controlled experiments are scanty, unreliable, and incapable of bearing the huge theoretical superstructure which has now been built up.

Implantation Dermoids

Q.—*A woman of 40 has had three implantation dermoids removed from her thumb in the past few months, and it appears that there may be more developing. Do some people show a tendency to develop this condition as other people do sebaceous cysts?*

A.—There is scarcely enough information given to answer this question fully, although there is certainly no known inherent tendency to the development of these lesions. Is it certain that the swellings were indeed implantation dermoids and that on each occasion there was unequivocal evidence of complete removal? Is the patient's occupation such that penetrating or punctured injuries are likely?

To distinguish them from true dermoids these cysts are now usually called "epidermoid." They may be congenital or traumatic in origin, and in the latter instance the interval between the trauma and the development of the cyst may be considerable. Congenital ones are unlikely in the hand, and so it is probable that the present case is post-traumatic. The injury is commonly, but not of necessity, a puncture, but in some cases there is no history of penetration and the cyst is thought to arise from the migration of epithelial cells from the sweat glands into a damaged area containing exudate or haematoma. If completely removed they do not recur, but as they may occasionally be multilocular the possibility of small islets of epithelium remaining must be considered as a cause of recurrence. Epidermoid cysts have rarely been reported in the bony phalanges, and, as the removal of the subcutaneous extensions of such a lesion would not be permanently curative, it would be as well to settle this question by radiography.

Modern Haemoglobinometry

Q.—*What are the more modern methods of carrying out a Hb estimation in the blood? What advantages have these over the Sahli method, and how accurate is the Sahli method compared with them?*

A.—The report of the Medical Research Council Subcommittee on analytical methods for the estimation of haemoglobin was recorded in a series of eight papers printed in the *Lancet*, of which three are pertinent.[1] In the first of these it was shown that the Haldane, Gowers, Sahli, Tallqvist, Tintometer, and Dare instruments were about equally inaccurate, one estimate out of twenty differing from the mean by 17% or more (coefficient of variation 8.5 to 10.9%). There was little to choose between these, but the Tallqvist was appreciably better than the Sahli. A series of wedge colorimeters were compared and these were markedly better, the coefficient of variation falling as low as 4.3% for oxyhaemoglobin. This led to the development of the M.R.C. photometer, and with this the coefficient of variation is much less, about 4½%.

All these are subjective methods depending finally on a colour matching or the matching of intensities of light. The M.R.C. photometer is quicker and easier to use than the Sahli method in addition to being much more accurate, but it is, of course, much more expensive. On the other hand,

it is sent out standardized by the National Physical Laboratory and requires no further standardization, so that results obtained with it by different observers can be directly compared. The M.R.C. photometer is unquestionably the best instrument for general use.

In large hospitals objective methods using photoelectric cells and galvanometers are more commonly used. Each of these instruments costs two or three times as much as the M.R.C. instrument and has to be calibrated. Standard analysed solutions of haemoglobin are now available, and most hospitals calibrate their instruments with such samples every few months. With a good photoelectric instrument and properly calibrated glassware the coefficient of variation is very small. With National Physical Laboratory grade A glassware my own instrument gives too small a variation to express in figures. With ordinary British Standard Specification 797 pipettes and a series of half a dozen different observers the coefficient of variation is about 2%. The photoelectric method has the great advantage of being much quicker to operate than any of the others, and, since it is not a subjective method, there can be no argument over the end-point. It is for these reasons that it remains so popular in hospitals.

REFERENCE

[1] *Lancet*, 1948, **1**, 282; **2**, 563, 971.

Ingrowing Eyelash

Q.—*A man of 40 has for two years had an ingrowing eyelash on the left lower lid which impinges on the eyeball and has to be plucked out. He does not wear glasses. Is there any way of preventing this eyelash from growing?*

A.—A single lash is best treated by electrolysis. This is likely to produce permanent epilation. A fine electrolysis needle attached to the negative pole is entered towards the root of the lash. The current used is 1 to 3 mA for 20 to 30 seconds. A bubble of white foam forms at the point of electrolysis. The procedure is best carried out after preliminary infiltration analgesia by 1 ml. of 4% procaine hydrochloride; it is, however, possible to dispense with this.

*** This answer is taken from the third book of *Any Questions?* Copies of the second and third books of *Any Questions?*, each containing some 200 expert answers, are available from the Publishing Manager, B.M.A. House, Tavistock Square, London, W.C.1, or through any bookseller, price 7s. 6d. a copy (postage 6d.). The third book contains a cumulative index.

Compatibility of Salts of the Same Drug

Q.—*Is there any pharmacological incompatibility between different salts of the same drug, such as streptomycin calcium chloride and streptomycin sulphate, either when given together or on succeeding occasions to the same patient?*

A.—In general there is no incompatibility between different salts of the same drug. But, if streptomycin calcium chloride were actually mixed together with streptomycin sulphate, there would be a precipitate of calcium sulphate. This would be undesirable for intrathecal injection, but would probably cause no trouble for intramuscular injection. No precipitation would occur if the two forms were given in successive doses, unless the time between the doses was very short and they were given at the same site.

Treatment of Dystrophia Myotonica

Q.—*What is the best treatment for securing muscular relaxation in a case of dystrophia myotonica?*

A.—Quinine hydrochloride by mouth in divided daily dose of 10–15 g. (0.65–1 g.) remains the treatment of choice for securing relaxation in dystrophia myotonica. At the present time procaine amide is under investigation in this connexion, but until further information is available its general use cannot be advocated. In any case, the main disability in dystrophia myotonica results from muscular weakness rather than myotonia.

Risk of Having a Second Mongol

Q.—*I should be grateful for your help with this problem. I have a patient, 32 years of age, who gave birth to a mongol six years ago. There is no mental abnormality on either side of the family. What are the chances of this woman having a normal child? There have never been any miscarriages or abortions, and this was her first and only child.*

A.—Familial incidence in mongolism is very low. There is probably a slightly increased chance that a woman who has had one affected child will have another. The risk also increases with age in any mother. This woman is relatively young and it is probable that the chance that another child would be affected is not greater than, say, one in a hundred.

NOTES AND COMMENTS

Aphthous Ulcers.—Dr. FREDERICK SUTTON (Bristol) writes: In "Any Questions?" (January 22, p. 242) your expert states that "the painting of [aphthous] ulcers with caustic cannot be recommended, since this usually prolongs the healing process and does not prevent the formation of further ulcers." If, however, the time-honoured measure be adopted—namely, that of touching the ulcers twice daily with 2% silver nitrate in spirit of nitrous ether—not only will the ulcers immediately become less painful but in the vast majority of cases they will quickly disappear. Only a very few patients require a 4% solution, and with either of these strengths argyria never occurs. Neither from the point of view of prophylaxis, nor from the point of view of treatment, have antibiotics or antihistamines proved to be of any real value. It should be pointed out, however, that, though the real cause is unknown, it is nevertheless true that such patients have a very sensitive mucosa, and even the trauma occasioned by a toothbrush may bring about a crop of ulcers. Therefore a very soft toothbrush should be used, or even none at all, the gums being gently swabbed with a pledget of wool on the finger dipped in a liquid dentifrice. "T.C.P." or some similar preparation, 2 dr. (7 ml.) in half a tumblerful of warm water as a gargle twice daily, may have a useful prophylactic influence, and if applied undiluted to the ulcers it may bring about healing, but not so rapidly as the silver preparations above mentioned.

OUR EXPERT writes: I do not think that I can usefully add much to my original reply, in which I made it clear that unfortunately the aetiology of the condition is still obscure and any local treatment is purely symptomatic. I agree with Dr. Sutton that painting the ulcers with silver nitrate, or touching with carbolic, may desensitize them slightly, but there is, I think, general agreement among people who see many of these cases that the further destruction of tissue and possible deepening of the ulcer may in fact delay healing. I agree entirely that antibiotics, administered either generally or locally, have no beneficial effect. But it is difficult to agree or disagree with the statement that patients have a very sensitive mucosa, since this is difficult to determine. I have never noticed any association of a hard toothbrush or trauma with the condition. Most frequently the ulcers occur in crops, and they are particularly prone to occur in females. It has been said that there is some connexion with monthly periods, but I have noticed myself over the years that this does not in fact appear to be the case, but, as women have periods, they form a sort of datum line although the crops of ulcers do not really fall into any definite pattern.

All communications with regard to editorial business should be addressed to THE EDITOR, BRITISH MEDICAL JOURNAL, B.M.A. HOUSE, TAVISTOCK SQUARE, LONDON, W.C.1. TELEPHONE: EUSTON 4499. TELEGRAMS: *Aitiology, Westcent, London.* ORIGINAL ARTICLES AND LETTERS forwarded for publication are understood to be offered to the *British Medical Journal* alone unless the contrary be stated.

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